CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212156Orig1s000

NON-CLINICAL REVIEW(S)

Memo to the Division File

NDA 212156 (SN-0016; SDN 16, SN-0018; SDN19, and SN-0019; SDN20) Micafungin for Injection, 50 mg/vial and 100 mg/vial (received December 12, 2020)

From: Kelly Brant, MPH, Ph.D., DABT, Pharmacology/Toxicology reviewer

Through: Terry Miller, Ph.D., Pharmacology/Toxicology supervisor

To: Eva Zuffova, PhD, MS

Subject: Resubmission/Class 2: Response to Complete Response Letter issued May 18, 2020

Date: June 1, 2021

Executive Summary: Micafungin for Injection does not contain any impurities, degradants, or extractables/leachables that are likely to pose a safety concern from a Pharmacology/Toxicology perspective. The nonclinical deficiencies identified in the May 18, 2020 Complete Response Letter regarding the proposed impurity acceptance criterion and leachables assessment have been adequately addressed. The acceptance criterion for impurities have been tightened to NMT (b)(4)%, with exception of Impurity (b)(4). The Applicant requested expanding the acceptance criterion of Impurity (b)(4) to NMT (b)(4)% based on 24- month stability data. The justification provided for the NMT (b)(4)% acceptance criteria, that Impurity (b)(4) which has been detected (b)(4) at levels ranging from (b)(4)% (b)(4) appears adequate. A (b)(4)-like leachable was detected at (b)(4) mcg/ml, which under worst-case scenario would result in daily exposures of (b)(4) mcg/day (1 to 3 vials). Given the (b)(4)-like leachable was only observed in 1 of 6 samples tested, and the worst-case scenario exposures are within the range of the 5 mcg/day safety threshold, the presence of the (b)(4)-like leachable is unlikely to pose any safety concerns. This is supported by the information provided in the risk assessment that was submitted by the Applicant. From a Pharmacology/Toxicology perspective, the NDA is recommended for approval.

Regulatory History: The original 505(b)(2) NDA submitted by the Applicant (Par Pharmaceutical) on November 19, 2018 received a refuse to file based on lack of drug product stability data. The Applicant resubmitted their NDA on July 18, 2019. A Complete Response Letter was issued on May 18, 2020 citing deficiencies regarding proposed acceptance criteria for identified impurities that were relevant to Pharmacology/Toxicology [see Nonclinical Review in DARRTS (April 30, 2020)]. Specifically, the proposed acceptance criterion for Impurity (b)(4) (NMT (b)(4)%), (b)(4) (NMT (b)(4)%) and any unspecified impurity (NMT (b)(4)%) were above the NMT 0.2% qualification threshold per ICH Q3B guidelines. In addition, there was insufficient information to determine the adequacy of the submitted leachables assessment (an amendment submitted late in the previous cycle was not reviewed for the CR action). The current submission, containing revised acceptance criterion for the identified impurities, additional leachables assessments and associated toxicological risk assessment on identified leachables, are reviewed below.

Nonclinical Deficiencies from the May 18, 2020 CR Letter

1. Provide your revised leachables assessment, including the toxicological assessment you planned to provide for [redacted] on July 31, 2020. The adequacy of your revised leachables study will be assessed at time of resubmission.

Applicant Response:

The Applicant incorporated by reference their April 6, 2020 revised leachable assessment (C124-REP-587.03) that was not reviewed by OPQ under the previous submission. The C124-REP-587.03 leachables report identified four inorganics not found in USP <232>: [redacted] which were detected at a concentration of [redacted] mcg/g. With a maximum daily dose of [redacted] g micafungin, this equates to [redacted] mcg/day. Given the maximum daily exposures of [redacted] associated with micafungin use are less than the 5 mcg/day safety threshold, they are not expected to pose a safety concern. This is supported by the Applicant's toxicological assessments of [redacted]. Permissible daily exposure levels (PDEs) and maximum allowable concentrations (MACs) of elements in the Micafungin for Injection drug product were derived using available toxicity information including regulatory/government exposure guidelines for sensitive populations (e.g., infants and patients with impaired kidney function). The estimated PDEs and MACs were adequately calculated and provide considerable safety margins to the maximum daily exposures of [redacted] associated with administration of the Micafungin for Injection drug product.

Table 8. Permitted Daily Exposures (PDEs) and Maximum Allowable Concentrations (MACs) of Elements in Micafungin Drug Product

Identity	CAS No.	$PDE_{parenteral}$ (µg/d)	$MAC_{drug\ product}$ (µg/g)
[redacted]			

Source: Toxicological Assessments of [redacted] and Development of Permitted Daily Exposure (PDE) Levels (page 44)

CMC issued an IR on February 22, 2021 asking the Applicant to provide the leachable data for the non-volatile, semi-volatile and inorganic impurities in the lyophilized powder of the aged drug product as this information was not included in the submitted leachable study report C124-REP-586.02. The Applicant submitted the requested information on April 29, 2021. Per communication with the drug product quality reviewer (Dr. Yang Nan), there was one leachable detected at above the analytical evaluation threshold (AET) of [redacted] mcg/mL, a non-volatile [redacted]-containing compound partially identified as a [redacted]. The [redacted]-containing compound was only detected at above the AET in one of the 50 mg/vial samples (a total of 6 batches were analyzed in the leachables study, 3 each of the 50 mg/vial and 100 mg/vial). The signal was less than that for the lowest reference standard of [redacted] mcg/mL. Using a worst-case scenario, one can assume the [redacted]-containing compound is present at [redacted] mcg/mL.

Micafungin for Injection is reconstituted in 5 mL of either 0.9% saline or 5% dextrose, which equates to an estimated exposure of [redacted] mcg of the [redacted]-containing compound/day (1 to 3 vials). Given the estimated daily exposures are comparable with the 5 mcg/day safety threshold and that the [redacted]-containing compound was only detected at above the AET in one sample, it is unlikely to pose a safety concern. This is supported by the information provided in the toxicological risk assessment (reviewed below).

Toxicological Assessment of a [redacted]-containing Compound as a Leachable in a Parenteral Drug Product (Micafungin for Injection)

No toxicity data were located for the [redacted]-containing compound. Alternative methods, including use of structurally similar surrogate compounds with available toxicity information, *in silico* methods to a) predict probable metabolites and b) predict mutagenicity of the target compound were used to predict toxicity associated with leachable exposure.

Over 30 genotoxicity, repeated-dose toxicity and reproductive and developmental toxicity studies were located for two structurally similar compounds: [redacted]

[redacted]

[redacted] The U.S. EPA established oral reference dose (RfD) for [redacted] mg/kg-d based on a 13-week oral toxicity study conducted in rats. The bulk of toxicity information available for [redacted] comes from ECHA registration dossiers[1]. Although much of the toxicity data contained in the ECHA dossiers are unpublished, there is considerable consistency in the reported findings across studies conducted by independent groups.

ADME. It is estimated that > 70% absorption occurs following oral administration of [redacted]. MultiCase META Ultra software predicted that little metabolism of the target compound is likely and that all

[redacted]

predicted primary metabolites are structurally similar to the target compound (and by extension, to [redacted]).

Genotoxicity. Although the levels of [redacted]-containing compound are < [redacted]mcg/day, the Applicant notes that OECD QSAR Toolbox (2021) identified no structural alerts for *in vitro* bacterial reverse mutagenicity, *in vivo* mutagenicity (micronucleus), or carcinogenicity. In addition, both [redacted] surrogate compounds were negative for mutagenicity and did not induce chromosomal aberration *in vitro* and were negative in vivo for bone marrow micronucleus formation and chromosomal aberrations in mice. While many of the original study reports were not available, negative findings were consistent across 4 to 6 independent in vitro and in vivo genotoxicity studies. No evidence of carcinogenicity was reported from 2-year dietary studies conducted in rat, dog and mouse.

Irritation/sensitization. [redacted] are non-sensitizing and were found to be non-irritating to mildly irritating in multiple guinea pig sensitization, rat and rabbit dermal and rabbit ocular irritation studies.

Repeated-dose Toxicity. Seventeen oral gavage or dietary studies ranging from 28 days to 2 years in duration have been conducted with [redacted] in mice, rat and dog. Detailed study findings are lacking in the ECHA dossiers with most study summaries just providing observed NOAELs and/or LOAELs. When reported, adverse findings across species were decreased body weight and body weight gains, increased liver weight and fatty degeneration of the liver, and renal tubule degeneration. NOAELs for [redacted] ranged from 86.9 to 450 mg/kg-day in the 28-day studies in rat, 6.4 to 26.9 mg/kg-day in 90-day studies in rat, mice and dog, and 3.8 to 5 mg/kg-day in a 2-year rat study. NOAELs reported for 2-year studies conducted with [redacted] were 27.25 to 29.45 mg/kg-day (rat), 142 mg/kg-day (mice) and 3.75 mg/kg-day (dog).

Reproductive and Developmental Toxicity. Two rat oral EFD studies conducted with [redacted] were described in the ECHA dossier. Once study reported a LOAEL of 30.6 mg/kg-day and another reported a LOAEL of 404 mg/kg-day. At high doses, maternal mortality, reduced maternal body weight gain, increased postimplantation death and reduced fetal weight were among the adverse findings reported. An increased incidence of malformed fetuses (litters) of up to 5.8% (29.4%) was also noted, however in the absence of full study reports it is not certain if these effects occurred in the absence of maternal toxicity. It is also uncertain as to why there is 10-fold difference in the reported LOAEL. One possible explanation could be the use of different rat strains in the two EFD studies, but this information was not provided.

Oral exposure to [redacted] during gestation in rats and rabbits resulted in decreased maternal body weight and decreased number of live litters; NOAELs were 50 mg/kg-day (rat) and 12 mg/kg-day (rabbit).

In a 2-generation oral gavage study in rats conducted with [redacted], no effects on reproduction or development were reported at any dose, including effects on pup survival parameters or fertility. The NOAELs for reproductive/development effects were 94.4 and 96.0 mg/kg-d for males in P and F_1 generations, respectively, and 126.4 and 132.8 mg/kg-d for females in P and F_1 generations, respectively. A separate 2-generation oral gavage study in rats conducted with [redacted] reported no teratogenic effects at doses up to 250 mg/kg-day.

In a 2-generation oral dietary study in rats conducted with (b) (4) decreased food consumption, body weight, and body weight gain were seen in the parental generation at ≥ 50 mg/kg-day. In F_1 pups, decreases in body weights were also seen at ≥ 50 mg/kg-day during lactation. The reported NOAEL was 0.65 mg/kg-day.

A LOAEL of 15 mg/kg-day was determined for (b) (4)-related effects on sperm (number per testis, daily sperm production, and Leydig cell number) in male rats following 56 days of oral (gavage) administration.

Based on the available toxicity information, a PDE_{oral} for the (b) (4)-containing leachable was derived using the NOAEL of 3.8 mg/kg-day (b) (4) from the 2-year oral diet study in rats, applying a modifying factor of (b) (4) (b) (4) for extrapolation of rats to humans, (b) (4) for intraindividual variability, (b) (4) for use of a chronic toxicity study, and (b) (4) for uncertainty surrounding severe systemic toxicity and use of (b) (4) as a toxicological surrogate):

(b) (4)

A $PDE_{parenteral}$ for the (b) (4)-containing leachable was derived by applying an additional modifying factor of 2 corresponding to an assumed oral bioavailability of ≥ 50% and < 90%:

$$PDE = \frac{(b)\ (4)\ mcg/day}{2} = (b)\ (4)\ \text{mcg/day}$$

Reviewer comment: The 2-generation oral dietary conducted with (b) (4) had a lower NOAEL of 0.65 mg/kg-day. Applying the same modifying factor of (b) (4) as above, using the 0.65 mg/kg-day NOAEL would yield a PDE_{oral} of (b) (4) mcg/day and $PDE_{parenteral}$ of (b) (4) mcg/day, equivalent to the worst-case scenario of 9.66 mcg/day exposure of the (b) (4)-containing leachable.

The Applicant also extrapolated maximum allowable concentrations (MACs) for the drug product based on the maximum dose of (b) (4) g/day, delivered for a usage duration of 10-30 days, mean of 15 days:

(b) (4)

For comparison, the Applicant also calculated an alternate $MAC_{drug\ product}$ of (b) (4) mcg/g using a Threshold of Toxicologic Concern (TTC) of (b) (4) mcg/day based on Cramer classifications of the identified surrogate compounds (i.e., Class III). The Agency has not adopted TTCs for leachables based on their Cramer classifications. However, the $PDE_{parenteral}$ of (b) (4) mcg/day calculated based on available toxicity information for the (b) (4) surrogate compound appears appropriate. The calculated value incorporates adequate modifying factors to capture uncertainties when deriving PDEs from surrogate toxicity data and provides a (b) (4)-fold margin over the 5 mcg/day safety threshold.

2. As noted in the product quality comments above, the proposed acceptance criterion for Impurity (b) (4) (NMT (b) (4)%), impurity at (b) (4) (NMT (b) (4)%) and any unspecified impurity (NMT (b) (4)%) are above the ICH Q3B qualification thresholds of NMT 0.2%. If the acceptance criterion cannot be tightened to NMT 0.2%, provide adequate characterization for impurity at (b) (4) and any unspecified impurity(ies), along with a comprehensive toxicological assessment for all impurities greater than 0.2% when

administered intravenously. If sufficient toxicity information is not available, additional nonclinical studies may be recommended to qualify the safety of impurities > 0.2%.

Applicant Response: The acceptance criterion for Impurity at (b) (4) and any unspecified impurity has been tightened to NMT (b) (4)%. Per communication with the drug product quality reviewer (Dr. Yang Nan), Impurity (b) (4) was out of the revised specification at 24 months for Micafungin Lot 308972/308975, 50 mg/vial (b) (4)%). The Applicant requested and provided adequate justification for expanding the Impurity (b) (4) specification from NMT (b) (4)% to NMT (b) (4)% (see Applicant's 5/13/2021 response to IR). Specifically, Impurity (b) (4) (also known as (b) (4) has been detected in (b) (4) at levels ranging from (b) (4) The Applicant states that repeated daily doses up to (b) (4) mg/kg (maximum total daily dose of (b) (4) mg) in adult patients have been administered in clinical studies with no reported dose-limiting toxicity. As such, it is inferred that increasing the shelf life specification for Impurity (b) (4) from (b) (4)% w/w to (b) (4)% w/w will have no detrimental effect in patients. As noted in ICH Q3A "Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified.[3]" This deficiency has been adequately addressed from a Pharmacology/Toxicology perspective; there are no outstanding safety concerns regarding the identified impurities in the Micafungin for Injection drug product.

Recommendation

From a Pharmacology/Toxicology perspective, the NDA is recommended for approval.

Upon review of the Applicant's response to the CR Letter nonclinical deficiencies and communication with the CMC reviewer, there are no impurities, degradants, or extractables/leachables associated with Micafungin for Injection that are likely to pose a safety concern from a Pharmacology/Toxicology perspective. As noted previously [see Nonclinical Review in DARRTS (April 30, 2020)], the Applicant is relying on the Agency's previous finding of safety and efficacy for the LD, Mycamine® (NDA 021506). Micafungin for Injection utilizes the same active ingredient, micafungin sodium, and indications and conditions of use are the same as that of the LD. The Applicant did not submit any new Pharmacology/Toxicology information in the NDA. The levels of excipients in Micafungin for Injection (i.e., sucrose) are at or below those found in other FDA approved products administered vis the same route and provide similar coverage regarding duration of therapy.

[3] https://www.fda.gov/media/71727/download

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/s/

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06/09/2021 04:47:06 PM

Memo to the Division File

NDA 212156 (S-0003) Micafungin for Injection, 50 mg/vial and 100 mg/vial

From: Kelly Brant, MPH, Ph.D., DABT, Pharmacology/Toxicology reviewer

Through: Terry Miller, Ph.D., Pharmacology/Toxicology supervisor

Date: April 21, 2020

Background: The original 505(b)(2) NDA submitted by the Applicant (Par Pharmaceutical) on November 19, 2018 was refused to file based on lack of drug product stability data. The Applicant resubmitted their NDA on July 18, 2019. The Applicant is relying on the Agency's previous finding of safety and efficacy for the LD, Mycamine® (NDA 021506). Micafungin for Injection utilizes the same active ingredient, micafungin sodium, and indications and conditions of use are the same as that of the LD.

The Applicant did not submit any new Pharmacology/Toxicology information in the NDA. No Pharmacology/Toxicology information was reviewed to support this NDA. The formulations of Micafungin for Injection, 50 mg/vial and 100 mg/vial contain different inactive ingredients compared with the LD. Both drugs contain citric acid and/or sodium hydroxide (for pH adjustment), however Micafungin for Injection contains sucrose (b) (4) whereas the LD uses lactose (see Table 1 below).

Table 1: Composition of Micafungin for Injection

Ingredient	Grade	Function	Par Composition (mg/vial)		LD Mycamine® Composition (mg/vial)	
Micafungin Sodium	N/A	Active Pharmaceutical Ingredient	50 mg	100 mg	50 mg	100 mg
Sucrose	NF	(b) (4)	200 mg (4% w/v)[b]	400 mg (8% w/v)[b]	N/A	N/A
Lactose	NF		N/A	N/A	200 mg	200 mg
Citric Acid	USP	pH Adjustment	QS	QS	QS	QS
Sodium Hydroxide	NF/EP	pH Adjustment	QS	QS	QS	QS
(b) (4)						

[b]Amount after reconstitution with 5 mL of diluent

Source: Applicant's Table 1, page 2 of 1.12.15

Micafungin for Injection 50 mg/vial contains 200 mg sucrose and Micafungin for Injection 100 mg/vial contains 400 mg sucrose, with a maximum daily exposure of 600 mg sucrose/day (based on maximum Micafungin dose of 150 mg/day, equivalent to 3 vials of 50 mg/vial). The exposure levels for sucrose are at or below those found in other FDA approved products administered via the same route and provide similar coverage regarding duration of therapy.

The Applicant conducted an admixture study to evaluate the pH, assay, impurities, and clarity in 3 lots of the 50 mg and 100 mg Micafungin for Injection diluted product compared with the LD. In addition, the Applicant provided comparative osmolality and tonicity for 5 lots of the LD and 6 lots of the Micafungin for Injection drug product. Per the Biopharmaceutics reviewer the data provided support the bridging between the proposed drug product and the LD (for details of the Biopharmaceutics assessment refer to the Office of Product Quality review by Dr. Akm Khairuzzaman).

Micafungin for Injection does not contain any novel excipients that warrant any new nonclinical studies.

Impurities

Per the Drug Product Review, the proposed acceptance criterion for Impurity (b) (4) (NMT (b) (4) %), (b) (4) (NMT (b) (4) %) and any unspecified impurity (NMT (b) (4) %) are above the qualification threshold. An IR was issued to the Applicant that they tighten the limit to NMT 0.2% per ICH Q3B guidelines or provide toxicology data to justify the proposed limits. The Applicant indicated that a full response would be provided to the Agency on July 31, 2020.

Leachables

In their leachables report submitted on March 25, 2020, the Applicant did not provide a justification for the analytical evaluation threshold (AET) of (b) (4) mcg/mL used for the leachables assessment. An IR was issued asking the Applicant was asked to provide a justification for (b) (4) mcg/mL AET. In their response, the Applicant stated that the original Analytical Exposure Threshold (AET) of (b) (4) mcg/mL was calculated using the Less-than-lifetime exposure levels per Section 7.3 of ICH M7(R1), with a threshold of toxicological concern (TTC) acceptable intake of 20 mcg/day (>1 to 12 months) assigned as the Safety Concern Threshold. The Applicant provided a revised leachables study using a newly calculated AET of (b) (4) mcg/ml using the recommended safety threshold of 5 mcg/day.

Reviewer comment: The Applicant used a value of (b) (4) mL in calculating the revised AET; however, the vials are reconstituted in 5 mL diluent. An AET calculated using the 5 mL would equal (b) (4) mcg/mL. An AET of (b) (4) mcg/mL equates to exposures between (b) (4) mcg/day (1 to 3 vials), below the 5 mcg/day safety threshold. Of note, the leachables assessment using the (b) (4) mcg/mL AET, the exposures related to drug product use also below the 5 mcg/day safety threshold (between (b) (4) mcg/day).

From a Pharmacology/Toxicology perspective, the leachables appear to be at or near the 5 mcg/day safety threshold. However, given the lateness of the submission (revised study was received on 4/6/2020) in the review cycle and the outstanding deficiencies regarding the impurity specifications and characterization, the CMC reviewer has indicated the leachables study will not be reviewed during this cycle (e-mail communication with CMC Reviewer Dr. Yang Nan and Dr. Andrei Ponta).

Recommendation

Pharmacology/Toxicology cannot recommend marketing approval for this application at this time due to unresolved issues regarding the leachables study and stability impurity specifications.

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/s/

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04/21/2020 12:23:02 PM

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