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APPLICATION NUMBER:

216142Orig1s000

NON-CLINICAL REVIEW(S)

Memo to the Division File

NDA 216142 (SN-01, SN-06, SN-07, SN-09)

Micafungin in 0.9% Sodium Chloride (Baxter Healthcare Corporation)

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

Through: Terry Miller, Ph.D., Deputy Division Director

To: Sheel Shah, Pharm.D., RPh

Subject: Review of NDA submission (impurities and leachables safety qualification)

Date: June 27, 2023

Executive Summary. From a Pharmacology/Toxicology perspective, the NDA is recommended for approval. Impurities detected in Micafungin in 0.9% Sodium Chloride at levels higher than the LD and ICH Q3B(R2) qualification threshold (i.e., Impurities (b) (4)) were adequately qualified for safety. In silico (Q)SAR analysis predicted the impurities to be negative for bacterial mutagenicity. Findings from the submitted 30-day impurity qualification toxicity study with bone narrow micronucleus evaluation in rat indicate that exposures to micafungin pre-mix containing the detected impurities were well tolerated at approximately 1- to 4-fold safety margins based on body surface area (BSA) comparisons and that the impurities were non-clastogenic. The Applicant also provided a comprehensive toxicological risk assessment that adequately qualified the leachables associated with the (b) (4) GALAXY container for safety, i.e., (b) (4) .
Based on the calculated permissible daily exposure (PDE) values for the individual leachable and/or surrogate compounds, safety margins ranged from 13 to > 3000-fold the anticipated clinical exposures in adult, pediatric and neonatal patients.

Background. The Applicant, Baxter Healthcare Corporation, submitted a 505(b)(2) NDA for a ready-to-use premixed Micafungin in 0.9% Sodium Chloride Injection product in (b) (4) GALAXY containers. The Applicant is relying on the Agency's previous findings of safety and efficacy for the LD MYCAMINE® 50 mg/vial and 100 mg/vial (NDA 021506). The proposed product strengths are 50mg/50 mL, 100 mg/100 mL, and 150 mg/150 mL micafungin, with (b) (4) in 0.9% sodium chloride. While the 150 mg/150 mL presentation represents a new total drug content from that of the LD, the dosing information in the approved MYCAMINE® prescribing information allows for single doses of 150 mg. The proposed micafungin premix formulation includes the same dosage form as administered, the same route of administration, the same drug substance micafungin sodium, and the use of the same diluent for infusion as that of the LD. The Applicant provided data supporting a scientific bridge between the proposed drug product and the LD, including a side-by-side quantitative and qualitative comparison of the two product formulations (Table 1). The proposed drug product specifications for Micafungin in 0.9% Sodium Chloride indicates specified impurities exceed both the ICH Q3B(R2) qualification threshold of 0.2% and the levels in the LD. The Applicant submitted an *in silico* (Q)SAR assessment, Ames assay, and 30-day impurity qualification toxicity study in rat (with bone marrow micronucleus evaluation) to qualify the specified impurities. The Applicant also provided a comprehensive toxicological risk assessment for leachables detected in the drug product at levels > 5 mcg/day safety threshold.

Table 1. Comparison of Micafungin in 0.9% Sodium Chloride and LD MYCAMINE®

Ingredient (Function)	Micafungin in 0.9% NaCl Injection (proposed formulation)			LD MYCAMINE® (NDA 021506)	
Citric Acid, Anhydrous, USP (b) (4)	0.72 mg/vial	0.72 mg/vial	0.72 mg/vial	N/A	N/A
Sodium Citrate, Dihydrate, USP (b) (4)	1.84 mg/vial	1.84 mg/vial	1.84 mg/vial	N/A	N/A
Lactose (b) (4)	N/A	N/A	N/A	200 mg/vial	200 mg/vial
Sodium Hydroxide, NF (pH Adjuster)	N/A	N/A	N/A	As Required	As Required
Citric Acid (pH Adjuster)	N/A	N/A	N/A	As Required	As Required
Water for Injection, USP (b) (4)	Quantity Sufficient	Quantity Sufficient	Quantity Sufficient	N/A	N/A
Administered Micafungin Concentration	1 mg/mL	1 mg/mL	1 mg/mL	0.5-4 mg/mL	0.5-4 mg/mL
pH	4.5-5.1	4.5-5.1	4.5-5.1	5-7	5-7
Container Closure System	Single-use GALAXY plastic container (50 mL)	Single-use GALAXY plastic container (100 mL)	Single-use GALAXY plastic container (150 mL)	Single-dose Glass Vial	Single-dose Glass Vial
Dosage form as marketed	Solution	Solution	Solution	Powder	Powder
Dosage form as administered	Solution	Solution	Solution	Solution	Solution
Route of Administration	Intravenous	Intravenous	Intravenous	Intravenous	Intravenous

N/A=Not Applicable

Source: Applicant table

Excipients. The proposed micafungin pre-mix formulation contains citric acid and sodium citrate whereas the LD contains lactose. Levels of citric acid and sodium citrate in the proposed pre-mix formulations are below the levels listed in the IID for FDA-approved products for intravenous administration and are not expected to pose any safety concerns from a Pharmacology/Toxicology perspective.

Impurities. The Applicant reports 9 impurities in Micafungin in 0.9% Sodium Chloride Injection requiring qualification for the proposed specification limits (see Table 2a and b). Structure identification was only provided for Impurities (b) (4) with the initial submission (SN-01 submitted 11/30/22). Because the maximum daily exposures to impurities at the desired qualification limit are (b) (4), an Information Request was sent to the Applicant on 04/07/23 to provide structural information for impurities (b) (4), along with (Q)SAR analysis for any structural alerts for mutagenicity as

per ICH M7(R1). In response to the IR, the Applicant provided additional MS/MS data and tentative structures for impurities (b) (4) (SN-07 and SN-09 submitted 04/14/23 and 5/31/23, respectively). Three of the impurities (b) (4) were determined to be (b) (4) , and four potential representative structures were proposed for use in (Q)SAR analysis (Table 2b).

Table 2a. Impurities in Micafungin in 0.9% Sodium Chloride Injection

Impurity Name	Structure	Desired Limit to be Qualified (%w/w)
(b) (4)		

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Although only a tentative structure was provided for (b) (4) with no structure provided for (b) (4) , the Applicant notes that (b) (4) is present in the LD at levels greater than the ICH Q3B(R2) qualification threshold of 0.2%. Moreover, the Applicant notes that the other 8 impurities observed in their proposed micafungin pre-mix formulation are also present in the LD at exposures (b) (4) [see Quality Information Amendment (SN 9 submitted 05/31/23) in DARRTS] (Table 3). While definitive structures for Impurities (b) (4) are not available, the proposed structures provided by the Applicant appear reasonable given the complexity of the micafungin API molecule [e-mail communication with Drug Product reviewer Hudson Roth (04/26/23)].

Table 3. MYCAMINE Impurity Exposure per Day

Impurity Name	Largest Value Observed in MYCAMINE at Expiry (%w/w)	Exposure* (mcg/day)
(b) (4)		

*Based on MDD of 150 mg
Source: Applicant

Although the impurities in the proposed pre-mix formulation are also present in the LD, the estimated clinical exposures are greater when considering the desired quantification limit (see Table 4 below).

Table 4. Clinical exposures to impurities detected in Micafungin for Injection

	Maximum Daily Exposure (mcg)*		
	Adult (60 kg)[1]	Pediatric > 4 months (up to 30 kg)[2]	Pediatric < 4 months (up to 6 kg)[3]
(b) (4)			

Source: Reviewer Table

To qualify the detected impurities at the desired limits noted in Table 2a, the Applicant conducted a 30-day repeated-dose general toxicity study in rat, which included an in vivo micronucleus assay. An Ames test was also carried out using the same batch of Micafungin premix used in the in vivo qualification study. Mutagenic potential was assessed in silico with the definitive and proposed impurity structures using two complementary (Q)SAR methodologies [an expert rule-based (Derek Prediction) and a statistical-based (Sarah Prediction) analysis per ICH M7(R1).

Study Title: Micafungin in 0.9% Sodium Chloride Injection: 30-Day Impurity Qualification Toxicity Study with Bone Marrow Micronucleus Evaluation in Sprague Dawley Rats/Study No. M-21318

Key Study Findings

- No test article (micafungin pre-mix containing impurities)-related toxicity was observed in animals following 30-day repeated dosing compared to the reference LD Mycamine®.
- The estimated daily exposures of the identified impurities in rats were approximately 1 to 4-times the estimated clinical exposures based on body surface area comparison (BSA).
- The test article (micafungin pre-mix containing impurities) did not induce micronucleated polychromatic erythrocytes in rats bone marrow and is considered non-clastogenic under conditions of the study.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes [OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM (98) 17, OECD, Paris, 1998].

Methods

Dose and frequency of dosing:	22.6 mg/kg/day for 30 days (micafungin) 40 mg/kg single dose on Day 30 (cyclophosphamide)
Route of administration:	Intravenous, 0.5 mL/min via lateral tail vein (micafungin) Oral gavage (cyclophosphamide)
Dose Volume:	29.4 mL/kg
Formulation/Vehicle:	G1: Micafungin premix in 0.9% NaCl (Baxter Batch No. 565266 2) G2: Micafungin in 0.9% NaCl [Mycamine® LD (Lot 029061)] G3: 0.9% NaCl (vehicle control) G4: cyclophosphamide (water)
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	10/sex/group G1-G3 5/sex/group G4
Age:	8-9 weeks
Deviation from study protocol affecting interpretation of results:	No

Observations and Results:

Parameters	Major findings
Mortality	None
Clinical Signs	None
Body Weights	None
Food Consumption	None
Ophthalmoscopy	No test article-related changes compared with LD and vehicle controls
Hematology	Slight increases in reticulocytes count (16-36%) were observed in test article- and reference LD-treated males compared with controls.
Coagulation	No test article-related changes in mean APTT and PT coagulation times compared with LD and vehicle controls
Clinical Chemistry	Male rats treated with micafungin (test article and LD) displayed increases in mean ALT (73-81%), AST (24-37%), and total bilirubin (34-44%) compared with vehicle controls. These changes are known effects of micafungin and were comparable between the test article and reference LD. All other clinical chemistry parameters were unremarkable.
Urinalysis	None
Gross Pathology	None
Organ Weights	No test article related changes were observed compared with LD and vehicle controls.
Histopathology Adequate battery: Yes Peer reviewed	Microscopic changes in liver (single cell necrosis) and spleen (extramedullary hematopoiesis) were observed in male rats treated with test article and reference LD compared with vehicle control, correlating with observed changes in ALT/AST and reticulocyte count, respectively.
Micronucleus Assessment	No induction of micronuclei in the immature erythrocytes was observed following 30-days repeated dosing with test article. The mean number of micronuclei present in the micafungin treated groups (1.8 to 2.20) were statistically and biologically comparable with the vehicle control group (1.8). The mean number of micronuclei for vehicle control was within the range of historical control data. Cyclophosphamide (positive control) induced a statistically significant increase in the mean number of micronuclei (16.60 to 17.00) that were within range of laboratory historical control data (8.425 to 20.318). The study is considered valid. Micafungin in 0.9% Sodium Chloride (containing Micafungin impurities) is considered non-clastogenic under conditions of the study.

Dose Formulation Analysis: Dose concentration analysis conducted on Day 1, Day 15, and Day 30 of dosing confirmed micafungin concentrations to be within 10% of nominal. No micafungin peaks were detected in any of the vehicle control samples. The test article formulation (Micafungin in 0.9% Sodium Chloride Injection) was also analyzed for Micafungin impurities and degradation products (known and unknown) prior to the initial study dose day and post the last study dose day using validated UPLC methods (see Table 5).

Table 5. Impurity concentrations (%w/w) in dose formulation analysis on Days 1 and 31 of dosing

Impurity	Micafungin for Injection premix Batch 565266 2 %w/w	Desired Limit to be Qualified % w/w
[redacted] (b) (4)		

Source: Appendix 18 of Study Report

Reviewer Assessment: The 30-day toxicity study was well conducted, and findings indicate the test article (premix Micafungin for Injection containing impurities) was well tolerated at the administered dose, achieving approximately 1 to 4-fold the MDD based on body surface area (BSA) comparisons (see Table 6). Of note, the Applicant calculated worst-case exposure to impurities in the adult patient population differently than the reviewer, considering a total dose of 4700 mg for treatment of candidemia and other Candida infections over 47 days (per the LD Mycamine® PI, the indicated treatment is 100 mg Micafungin for 47 days). The Applicant then calculated an equivalent exposure of [redacted] (b) (4) over a 30-day exposure ([redacted] (b) (4)) or [redacted] (b) (4) for 60 kg adult. Although a different approach was used by the reviewer to estimate maximum daily exposures, the resulting safety margins achieved in the rat study were comparable and adequate exposure margins were achieved.

Table 6. Impurities safety margins achieved in rat following 30-days of repeated dosing with micafungin for injection.

Impurity	Daily Exposure (mcg/kg)				Safety Margin[2]		
	Rat[1]	Adult 60 kg	Pediatric 30 kg	< 4 mo. up to 6 kg	Adult 60 kg	Pediatric 30 kg	< 4 mo. up to 6 kg
[redacted] (b) (4)					3.9	3.2	2.1
					2.4	2.0	1.3
					4.0	3.3	2.1
					1.7	1.4	0.9
					1.5	1.3	0.8
					1.4	1.1	0.7
					1.1	0.9	0.6
					1.3	1.1	0.7
					2.7	2.3	1.5
[redacted] (b) (4)							

Source: Reviewer Table

Study Title: Ames Bacterial Reverse Mutation Assay, Chemical Test Article (ISO)

Study no.:	BWQ128-GE02
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes (21 CFR 58)
Drug, lot #, and % purity:	Micafungin in 0.9% Sodium Chloride Injection Batch # 565266 2

Methods

Strains:	*S. typhimurium* TA98, TA100, TA1535, and TA1537 and *E. coli* WP2 *uvr*A
Concentrations in definitive study:	0.1 mL test article/plate
Basis of concentration selection:	Not specified
Negative control:	0.9% Sodium Chloride
Positive control:	(-S9) TA1535, TA100: Sodium azide (5 mcg/plate) TA97a: IC-191 Acridine (1 mcg/plate) TA98: 2-Nitroflourene (1.5 mcg/plate) WP2 (*uvr*A): 4-nitroquinoline 1-oxide (0.5 mcg/plate) (+S9) TA98, TA100, TA1535, TA97a: 2-Aminoanthracene (2AA) (5 mcg/plate) WP2 (*uvr*A): 2AA (30 mcg/plate)
Formulation/Vehicle:	0.9% Sodium Chloride
Incubation & sampling time:	48-72 hr at 37°± 2° C
Comment on Study Validity:	Study is valid: genotypes were confirmed for all tester strains, solvent controls were within historical control limits, all positive controls elicited significant increase in the number of revertant colonies.

Results

Batch No. 565266 2 of Micafungin in 0.9% Sodium Chloride Injection containing impurities listed in Table 2 was negative in the bacterial reverse mutation assay under test conditions used in this study.

No cytotoxicity or precipitate was observed nor were there any increases in revertant colonies in any of the tester strains at the volume of test article tested (0.1 mL) in the presence or absence of metabolic activation. However, only one concentration of Micafungin for Injection containing < 5 mcg of the individual impurities to be qualified was evaluated (see Table 7 below). The Ames test, as submitted, is not adequate to inform on mutagenic potential of the unknown impurities, which have estimated clinical exposures of (b) (4) mcg/day (see Table 4). However, (Q)SAR analysis conducted by the Applicant, and a separate analysis conducted by the CDER Computational Toxicology Consult Service (CTCS), predicted the impurities to be negative for bacterial mutagenicity.

Table 7. Impurity levels tested in Ames assay

Impurity ID	mcg/plate[1]
(b) (4)	

[1]Impurity levels reflect those detected in Micafungin in 0.9% Sodium Chloride Injection Batch No. 565266 2; per Study Report, 0.1 mL of 1 mg/mL test article was used per plate

Source: Reviewer

Based on the absence of toxicity observed in the repeated-dose study, the negative in vivo micronucleus assay, and (Q)SAR analysis, impurities in the proposed micafungin premix formulation have been adequately qualified for safety at the desired specification limits.

Leachables. The Applicant conducted three leachable studies on two product codes of Micafungin 0.9% NaCl Injection stored in a Galaxy (b) (4) Bag, 50 mg/50 mL and 150 mg/150 mL. A total of 9 leachables with maximum daily exposures (b) (4) were identified in the micafungin pre-mix solution. Worst case scenarios of patient exposures based on leachables detected under real-use conditions (5°C) for 9 months, 25°C for 6 months plus 5°C for 3 months, or 5°C for 12 months are shown in **Table 8.**

Table 8. Worst-Case Daily Exposure to Leachables Identified in Micafungin 0.9% NaCl Injection

Leachable	CASRN	Maximum Concentration (mcg/L)	Maximum Exposure (mcg/day)*
(b) (4)			

*based on 150 mg MDD and micafungin concentration of 1 mg/mL

Source: Reviewer Table

The Applicant evaluated the 3 leachables with patient exposure (b) (4) for bacterial mutagenicity using (Q)SAR as per ICH M7(R1) using the most recent versions of the software (i.e., Derek Nexus v 6.2.1 and Sarah Nexus v 3.2.1). (b) (4) were predicted to be negative for bacterial mutagenicity.

The Applicant also provided a comprehensive toxicological risk assessment that included read-across analysis with select surrogate compounds to determine a permissible daily exposure (PDE) and margin

of safety for the identified leachables. Seven of the nine leachables detected are (b) (4) anticipated to undergo (b) (4) (**Table 9**). For the (b) (4) leachables, the Applicant proposed a grouping strategy using the (b) (4) as surrogates for read-across for the entire group.

Table 9. (b) (4)

Leachable	(b) (4)

CTCS reviewed the Applicant's proposed grouping strategy and surrogate compounds and found the use of (b) (4) as surrogate compounds to be reasonable, with the exception of (b) (4), which is not a direct metabolite of any of the leachables and is, therefore, less relevant. CTCS also recommended that instead of the proposed grouping approach, that the corresponding (b) (4) for each (b) (4) are used to ensure that the most relevant surrogates are used for each leachable. (b) (4) was proposed as an additional surrogate as it is a (b) (4) that is expected to more closely match the bioavailability of (b) (4) leachables.

It is also of note that Batch No. 565266 2 of the micafungin pre-mix used in 12 months leachables study is the same batch used in 30-day qualification toxicity study in rats. As noted above, findings indicate the test article (micafungin pre-mix solution containing impurities and leachables) was well tolerated at the administered dose of (b) (4), approximately 1.4-fold the MDD based on body surface area comparisons.

Greater safety margins are afforded when considering PDE associated with the leachables and/or surrogate compounds (**Table 10**). The risk assessment conducted by the applicant utilized leachable exposure values applicable to the pediatric population < 4 months of age with MDD of 4 mg/kg/d as the worst-case exposure for all patient populations. The reviewer also calculated safety margins for adult

patients considering an MDD of 150 mg and pediatric patients > 4 months of age weighing ≤ 30 kg considering an MDD of 3 mg/kg/d. A detailed evaluation of available toxicity data for the detected leachables, surrogate compounds, and calculations of permissible daily exposures (PDE) for each compound are provided in **Tables 11 and 12**. Unless otherwise indicated, the applicant proposed surrogate was considered to be adequate. Based on the significant safety margins across patient populations and lack of predicted bacterial mutagenicity, leachables detected in the micafungin pre-mix formulation are not expected to pose a safety concern and are considered qualified.

Table 10. Leachables safety margins across patient populations

Leachable	Adult[1]			Pediatric[2] > 4 mo. of age ≤ 30 kg			Neonate[3] < 4 mo. of age		
	Max Exp (mcg/d)	PDE (mcg/d)	Safety Margin	Max Exp (mcg/d)	PDE (mcg/d)	Safety Margin	Max Exp (mcg/d)	PDE (mcg/d)	Safety Margin
(b) (4)			2000			2000			1500
			3191			3191			2394
			3704			3704			2778
			1216			1216			912
			3333			3333			2500
			276			276			207
			984			984			738
			3546			3546			2660
			17			17			13

[1]based on 150 mg MDD with 50 kg bw used for PDE calculation
[2]based on 3 mg/kg MDD (esophageal candidiasis) with 30 kg bw used for PDE calculation
[3]based on 4 mg/kg MDD with 6 kg bw used for PDE calculation

Source: Reviewer table

Table 11. Reviewer assessment of Toxicological Assessment of Leachables for Micafungin in 0.9% Sodium Chloride Injection

(b) (4)

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(b) (4)

Per the CTCS consult, it is recommended that the corresponding (b) (4) for each (b) (4) be used to ensure that the most relevant surrogates are used for each leachable. As such, for each of the (b) (4), the reviewer used the most conservate PDE for the (b) (4) (s) to calculate safety margins (see **Table 12**).

(b) (4)

Table 12. Surrogates and associated PDEs used to calculate safety margins for (b) (4) leachables

Leachable	Surrogate used	PDE (mg/day) for 50 kg adult
(b) (4)		

Labeling. Pharmacology/Toxicology does not have any suggested edits for the proposed labeling. The applicant has harmonized language in Sections 8 and 13 with the LD package insert (NDA 021506 rev 12/2019). A review of the published literature conducted by the applicant for non-clinical reproductive and developmental toxicity data, carcinogenicity, and genotoxicity (since December 20, 2019 – present) did not yield any results.

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KELLY A BRANT
08/31/2023 12:56:13 PM

TERRY J MILLER
09/13/2023 05:31:25 PM