Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	August 30, 2024
Reviewer:	Ivone Kim, MD Division of Pharmacovigilance I
Team Leader:	Carmen Cheng, PharmD Division of Pharmacovigilance I
Division Director:	Monica Muñoz, PharmD, PhD, BCPS Division of Pharmacovigilance I
Product Name:	Mycamine (micafungin for injection)
Pediatric Labeling Approval Date:	December 20, 2019
Application Type/Number:	NDA 021506
Applicant:	Astellas Pharma U.S., Inc.
TTT Record ID:	2024-9489

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mycamine (micafungin) injection for intravenous use in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with micafungin in pediatric patients.

Mycamine (micafungin) injection for intravenous use was first approved on March 15, 2005. At initial approval Mycamine was indicated for treatment of patients with esophageal candidiasis and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

On June 21, 2013, FDA approved extending the indication to include treatment of adult and pediatric patients 4 months and older for candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscess; esophageal candidiasis; and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

On December 20, 2019, FDA approved extending the micafungin indication again to include 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.

Currently, Mycamine is approved for the following indications in adult and pediatric patients:

- 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

This pediatric postmarketing safety review was prompted by the December 20, 2019, pediatric labeling for micafungin.

On February 26, 2016, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for micafungin in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with micafungin. On April 12, 2016, OSE's evaluation was presented to the Pediatric Advisory Committee (PAC) and the PAC agreed with OSE's recommendation.

DPV reviewed all U.S. serious FAERS reports with micafungin in pediatric patients less than 17 years of age from September 1, 2015 – May 14, 2024. DPV reviewed 42 U.S. serious reports with micafungin; however, all 42 reports were excluded from further discussion.

Overall, there were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with micafungin in pediatric patients less than 17 years of age.

DPV did not identify any new pediatric safety concerns for micafungin at this time and will continue routine pharmacovigilance monitoring for micafungin.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mycamine (micafungin) injection for intravenous use in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with micafungin in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Mycamine (micafungin) injection for intravenous use was first approved on March 15, 2005. At initial approval Mycamine was indicated for treatment of adult patients with esophageal candidiasis and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.[1]

On June 21, 2013, FDA approved extending the indication to include treatment of adult and pediatric patients 4 months and older for candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscess; esophageal candidiasis; and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.[2]

On December 20, 2019, FDA approved extending the micafungin indication again to include 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.[3]

Currently, Mycamine is approved for the following indications in adult and pediatric patients:[4]

- 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

This pediatric postmarketing safety review was prompted by the December 20, 2019, pediatric labeling for micafungin.

On February 26, 2016, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for micafungin in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with micafungin. On April 12, 2016, OSE's evaluation was presented to the Pediatric Advisory Committee (PAC) and the PAC agreed with OSE's recommendation.[5]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Mycamine (micafungin) injection labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional micafungin labeling information, please refer to the full prescribing information.[4]

---------- CONTRAINDICATIONS ----------
MYCAMINE is contraindicated in persons with known hypersensitivity to micafungin sodium, any component of MYCAMINE, or other echinocandins. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Hypersensitivity Reactions: Anaphylaxis and anaphylactoid reactions (including shock) have been observed. Discontinue MYCAMINE and administer appropriate treatment. (5.1)
- Hematological Effects: Isolated cases of acute intravascular hemolysis, hemolytic anemia and hemoglobinuria have been reported. Monitor rate of hemolysis. Discontinue if severe. (5.2)
- Hepatic Effects: Abnormalities in liver tests; isolated cases of hepatic impairment, hepatitis, and hepatic failure have been observed. Monitor hepatic function. Discontinue if severe dysfunction occurs. (5.3)
- Renal Effects: Elevations in BUN and creatinine; isolated cases of renal impairment or acute renal failure have been reported. Monitor renal function. (5.4)
- Infusion and Injection Site Reactions can occur including rash, pruritus, facial swelling, and vasodilatation. Monitor infusion closely, slow infusion rate if necessary. (2.5, 5.5)

---------- ADVERSE REACTIONS ----------
- Most common adverse reactions across adult and pediatric clinical trials for all indications include diarrhea, nausea, vomiting, abdominal pain, pyrexia, thrombocytopenia, neutropenia, and headache. (6.1)
- In pediatric patients younger than 4 months of age, the following additional common adverse reactions were reported at an incidence rate of ≥15%: sepsis, acidosis, anemia, oxygen saturation decreased and hypokalemia. (6.1)

8.4 Pediatric Use

Pediatric Patients 4 Months of Age and Older
The safety and effectiveness of MYCAMINE for the treatment of esophageal candidiasis, candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses, esophageal candidiasis, and for prophylaxis of Candida infections in patients undergoing HSCT have been established in pediatric patients 4 months of age and older. Use of MYCAMINE for these indications and in this age group is supported by evidence from adequate and well-controlled studies in adult and pediatric patients with additional pharmacokinetic and safety data in pediatric patients 4 months of age and older [see *Indications and Usage* (1), *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), and *Clinical Studies* (14)].

Pediatric Patients Younger than 4 Months of Age
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*

The safety and effectiveness of MYCAMINE for the treatment of candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses ***without*** meningoencephalitis and/or ocular dissemination at a dosage of 4 mg/kg once daily have been established in pediatric patients younger than 4 months of age. This use and dosage of MYCAMINE are supported by evidence from adequate and well-controlled studies in adult and pediatric patients 4 months of age and older with additional pharmacokinetic and safety data in pediatric patients younger than 4 months of age [see *Adverse Reactions* (6.1) and *Clinical Pharmacology* (12.3)].

Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses With Meningoencephalitis and/or Ocular Dissemination in Pediatric Patients Younger Than 4 Months of Age

The safety and effectiveness of MYCAMINE have ***not*** been established for the treatment of candidemia ***with*** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age.

In a rabbit model of hematogenous Candida meningoencephalitis (HCME) with Candida albicans (minimum inhibitory concentration of 0.125 mcg/mL), a decrease in mean fungal burden in central nervous system (CNS) compartments assessed as the average of combined fungal burden in the cerebrum, cerebellum, and spinal cord relative to untreated controls, was observed with increasing micafungin dosages administered once daily for 7 days. 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 [see *Microbiology* (12.4)]. In this rabbit model, micafungin concentrations could not be reliably detected in cerebrospinal fluid (CSF). Due to limitations of the study design, the clinical significance of a decreased CNS fungal burden in the rabbit HCME model is uncertain.

A randomized controlled trial evaluated a MYCAMINE dose regimen of 10 mg/kg once daily in pediatric patients younger than 4 months of age with suspected or proven *Candida* meningoencephalitis. Fungal-free survival at 1 week after end of therapy was observed in 60% of MYCAMINE-treated vs. 70% of amphotericin B-treated patients, and all-cause mortality was 15% vs. 10%, respectively. However, because this study was terminated early and enrolled only 30 pediatric patients younger than 4 months of age (20 treated with MYCAMINE and 10 treated with amphotericin B) which was 13% of the planned enrollment for the study, no conclusions can be drawn regarding efficacy of MYCAMINE at this dose regimen.

In six uncontrolled, open-label studies, and a neonatal intensive care unit (ICU) medical records database, pediatric patients younger than 4 months of age with suspected *Candida* meningoencephalitis or disseminated candidemia received MYCAMINE at dose regimens ranging from 5 to 15 mg/kg once daily. Across the entire MYCAMINE development program, only 6 pediatric patients with proven *Candida* meningoencephalitis were treated with dosages of 2 mg/kg, 8 mg/kg and 10 mg/kg once daily. Micafungin was detected in the CSF of pediatric patients with suspected *Candida* meningoencephalitis. No conclusions regarding the efficacy of a particular dosage of MYCAMINE or the penetration of micafungin into the CSF can be drawn due to limitations of the data, including but not limited to, multiple confounding factors, variable study designs, and limited numbers of patients. No new safety signals were observed with the use of MYCAMINE at dosages of 5 to 15 mg/kg once daily in pediatric patients younger than 4 months of age, and there was no discernible dose-response for adverse events.

Although the dosage for the treatment of candidemia with meningoencephalitis has not been established, antifungal activity in various CNS compartments in the rabbit HCME model and limited clinical trial data suggest that in patients younger than 4 months of age, dose regimens 10 mg/kg once daily or higher may be necessary for the treatment of candidemia with meningoencephalitis. Safety data from clinical studies for MYCAMINE at dose regimens of 10 to 15 mg/kg once daily in pediatric patients younger than 4 months of age did not reveal new safety signals.

Treatment of Esophageal Candidiasis and Prophylaxis of Candida Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation in Pediatric Patients Younger Than 4 Months of Age

The safety and effectiveness of MYCAMINE in pediatric patients younger than 4 months of age have not been established for the:

- Treatment of esophageal candidiasis
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	May 15, 2024
Time period of search	September 1, 2015† - May 14, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Micafungin sodium
MedDRA search terms (Version 27.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Data-lock date from OSE's previous pediatric postmarketing pharmacovigilance and drug utilization review of micafungin. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

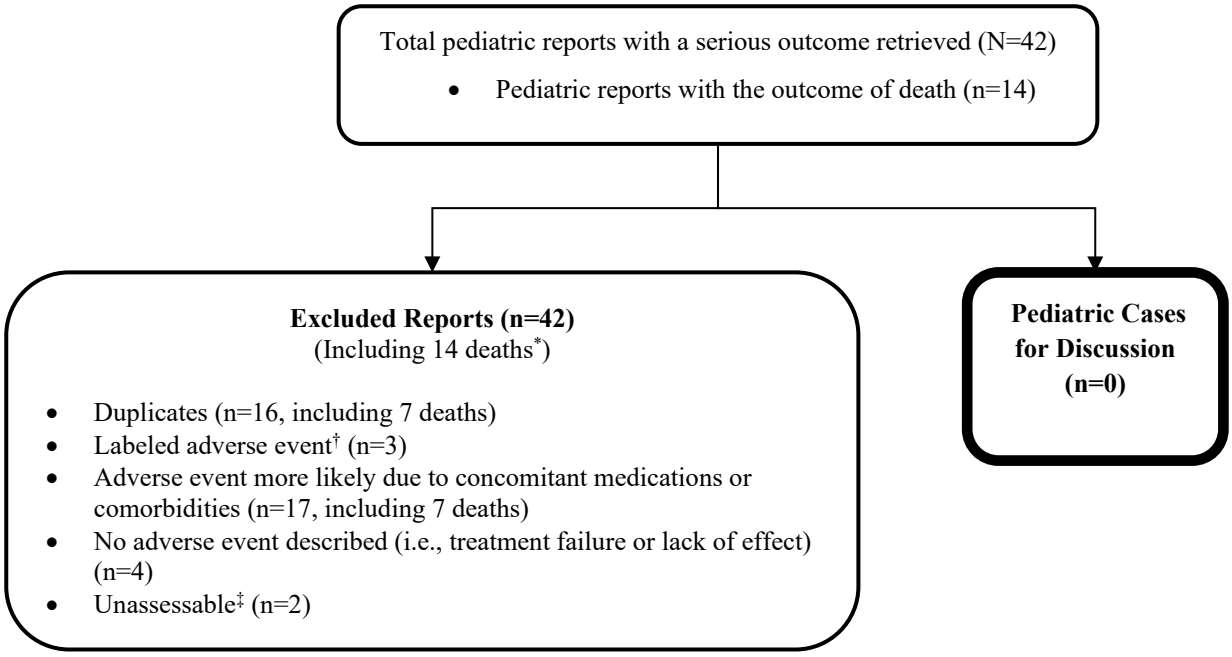
Table 2 presents the number of adult and pediatric FAERS reports from September 1, 2015 – May 14, 2024, with micafungin.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From September 1, 2015 – May 14, 2024, With Micafungin			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	1,695 (668)	1,523 (502)	605 (205)
Pediatrics (0 - < 17 years)	221‡ (49)	213‡ (42)	63‡ (14)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. ‡ See Figure 1. Two additional reports of U.S. pediatric deaths were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.			

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 42 U.S. serious pediatric reports from September 1, 2015 – May 14, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 42 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Micafungin



* Fourteen excluded U.S. FAERS reports described fatal outcomes. After accounting for duplicate reporting, DPV identified 7 unique cases with fatal outcomes. Five cases described patients with neoplastic disease who died from disease progression. One case described a neonate who died from complications of extreme prematurity. The last case described a patient who died from complications of COVID-19 infection and newly diagnosed type 1 diabetes mellitus in diabetic ketoacidosis. None of the deaths were determined to be attributed to micafungin.

† Labeled adverse event does not represent increased severity or frequency.

‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with micafungin in pediatric patients less than 17 years of age from September 1, 2015 – May 14, 2024. DPV reviewed 42 U.S. serious reports with micafungin; however, all 42 reports were excluded from further discussion.

Overall, there were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with micafungin in pediatric patients less than 17 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for micafungin at this time and will continue routine pharmacovigilance monitoring for micafungin.

6 REFERENCES

1. Mycamine (micafungin sodium) for injection. [Prescribing information]. Deerfield, IL; Fujisawa Healthcare, Inc.: March 2005.
2. Mycamine (micafungin sodium) for injection. [Prescribing information]. Northbrook, IL; Astellas Pharma US, Inc.: June 2013.
3. Approval letter. NDA 21506/S025. December 20, 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/021506Orig1s023ltr.pdf
4. Mycamine (micafungin injection) for intravenous use. [Prescribing information]. Northbrook, IL; Astellas Pharma US, Inc.: December 2019.
5. Pediatric Advisory Committee Meeting Minutes. April 12, 2016. Available at: https://www.fda.gov/media/97522/download

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.