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

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	February 26, 2016
Safety Evaluator:	Timothy Jancel, PharmD, BCPS (AQ-ID) Division of Pharmacovigilance II (DPV II)
Drug Use Analyst:	LCDR Justin Mathew, PharmD Division of Epidemiology II (DEPI II)
Team Leaders:	Kelly Cao, PharmD Division of Pharmacovigilance II (DPV II) Rajdeep Gill, PharmD Division of Epidemiology II (DEPI II)
Deputy Directors:	S. Christopher Jones, PharmD, MS, MPH Division of Pharmacovigilance II (DPV II) LCDR Grace Chai, Pharm.D Division of Epidemiology II (DEPI II)
Product Name(s):	Mycamine® (micafungin)
Pediatric Labeling Approval Date:	June 21, 2013
Application Type/Number:	NDA 021506
Applicant/Sponsor:	Astellas
OSE RCM #:	2015-1945

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Mycamine® (micafungin) in pediatric patients.

Mycamine® (micafungin) is an intravenous echinocandin initially approved on 16-Mar-2005 for the treatment of patients with esophageal candidiasis, and the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. On 21-Jun-2013, a product labeling revision was approved that altered the patient population to include pediatric patients:

> Mycamine® is an echinocandin indicated in adult and pediatric patients 4 months and older for: treatment of patients with candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses; treatment of patients with esophageal candidiasis; and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

The majority of the nationally estimated number of patients with a hospital billing for micafungin were adults 17 years and older, accounting for approximately 96% (104,000 patients) of total patients during the examined time period. Pediatric patients aged 0-16 years accounted for 4% (4,000 patients) of total patients. Among the pediatric patients, 58% (2,300 patients) were aged 2-11 years, 29% (1,147 patients) were aged 12-16 years, and 14% (562 patients) were aged 0-1 years.

The Food and Drug Administration Adverse Event Reporting System (FAERS) database was searched for serious adverse event reports associated with micafungin from 16-Mar-2005 through 31-Aug-2015. The FAERS review focused on the serious pediatric reports and a case series was established by the identification of all pediatric cases with fatal outcomes (n=12) or those with serious and unlabeled adverse events (n=10).

Overall, there were no patterns or trends in drug utilization or in the FAERS case series to suggest a new safety signal was associated with micafungin. The FAERS cases were either of poor quality or highly confounded making it difficult to assess a causal relationship between micafungin and the reported adverse events. The reported adverse events are likely due to underlying disease processes, concurrent disease states or medications, or other coincidental factors. However, a contributory role played by micafungin could not be excluded.

In summary, the reported adverse events were consistent in nature with the risks cited in the micafungin product label; no increased severity was observed in these reports. There is no evidence from these data to suggest that there are new pediatric safety concerns with micafungin at this time.

Based on the data summarized in this review, DPV does not recommend any labeling changes at this time. DPV will continue routine monitoring of the adverse event reports associated with the use of micafungin.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Mycamine® (micafungin) is an intravenous echinocandin initially approved on 16-Mar-2005 for the treatment of patients with esophageal candidiasis and for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.[1]

This PREA and BPCA review was triggered as a result of a product labeling revision on 21-Jun-2013 that expanded the indications from adults to pediatric patients.

Mycamine® is an echinocandin indicated in adult and pediatric patients 4 months and older. The most recently approved DOSAGE AND ADMINISTRATION section of the Mycamine® (micafungin) product labeling is presented in Table 1.1.[2]

Table 1.1 Recommended Dose Once Daily By Indication

Indication	Dose		
	Adult	**Pediatric ≤ 30 mg**	**Pediatric > 30 kg**
Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses	100 mg daily	2 mg/kg/day (maximum 100 mg daily)	
Treatment of Esophageal Candidiasis	150 mg daily	3 mg/kg/day	2.5 mg/kg/day (maximum 150 mg daily)
Prophylaxis of *Candida* Infections in Hematopoietic Stem Cell Transplant Recipients	50 mg daily	1 mg/kg/day (maximum 50 mg daily)	

Safety and effectiveness in pediatric patients 4 months and older have been demonstrated based on the evidence from adequate and well-controlled studies in adult and pediatric patients and additional pediatric pharmacokinetic and safety data. Safety and effectiveness in pediatric patients < 4 months have not been established.[2]

The overall safety of micafungin was assessed in 479 patients 3 days through 16 years of age who received at least one dose of micafungin in 11 separate clinical studies. The mean treatment duration was 24.8 days. A total of 246 patients received at least one dose of micafungin 2 mg/kg or higher. In all pediatric studies with micafungin, 439/479 (92%) patients experienced at least one treatment-emergent adverse event compared to 2497/2748 (91%) in adult patients. Although the overall incidence of treatment-emergent adverse events was similar between adults and children exposed to micafungin, abdominal pain, mucositis, rash, hypertension, and pruritus were more common in children than in adults. The frequency of serious adverse events was similar between pediatric patients (28%; 133/479) and adult patients (28%; 760/2748). There were no serious adverse events in pediatric patients that exceeded 5%.[1,2]

1.2 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS

There are no previous or current DPV reviews that are pending regulatory action for micafungin.

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current Mycamine® (micafungin**)** product labeling provides the following information excerpted from the pertinent sections (updated 21-Jun-2013).[2]

----------CONTRAINDICATIONS----------

Mycamine is contraindicated in persons with known hypersensitivity to micafungin sodium, any component of Mycamine, or other echinocandins.

----------WARNINGS AND PRECAUTIONS----------

Hypersensitivity Reactions

- Anaphylaxis and anaphylactoid reactions (including shock) have been observed. Discontinue Mycamine and administer appropriate treatment

Hematological Effects

- Isolated cases of acute intravascular hemolysis, hemolytic anemia and hemoglobinuria have been reported

Hepatic Effects

- Abnormalities in liver function tests; isolated cases of hepatic impairment, hepatitis, and hepatic failure have been observed

Renal Effects

- Elevations in BUN and creatinine; isolated cases of renal impairment or acute renal failure have been reported

Monitor closely patients who develop clinical or laboratory evidence of the above reactions and evaluate risk/benefit of continuing Mycamine therapy.

----------ADVERSE REACTIONS----------

- Most common adverse reactions include diarrhea, nausea, vomiting, pyrexia, thrombocytopenia, and headache
- Histamine-mediated symptoms including rash, pruritus, facial swelling, and vasodilatation

----------DRUG INTERACTIONS----------

Monitor for sirolimus, itraconazole or nifedipine toxicity, and dosage of sirolimus, itraconazole or nifedipine should be reduced, if necessary

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy - No human data. Adverse effects in animals. Use if potential benefits of treatment outweigh potential fetal risk
- Nursing Mothers -Caution should be exercised if administered to a nursing woman
- Safety and effectiveness in pediatric patients less than 4 months of age have not been established

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

2.1.1 Determining Settings of Care

Proprietary drug utilization databases were used to conduct this analysis.

The IMS Health, IMS National Sales Perspectives™ database (see Appendix A for full database descriptions) was used to determine sales of micafungin to various settings of care. During year 2014, micafungin sale by number of bottles sold from the manufacturer indicated that greater than 99% was distributed to the non-retail pharmacy settings, and less than 1% to retail pharmacy setting and mail-order/specialty pharmacies.[3] As a result, non-retail pharmacy utilization patterns were examined. Retail pharmacies and mail-order/specialty settings data were not included in this analysis.

2.1.2 Data Sources Used

The IMS Health, Inpatient HealthCare Utilization System (ICHarUS) database was used to obtain the nationally estimated number of patients who had a hospital discharge billing for micafungin in the U.S. non-federal hospital inpatient and outpatient ER setting, stratified by patient age (0-16 years and 17 years and older), from September 2010 through August 2015.

2.2 RESULTS

2.2.1 Number of Patients With an Inpatient and/or Outpatient ER Hospital Billing for Micafungin

Table 2.2.1 provides the nationally estimated number of patients with an inpatient and outpatient ER hospital billing for micafungin, stratified by patient age, from September 2010 through August 2015, annually. Nearly 83,000 patients had a hospital billing for micafungin in 12-month period ending in August 2011. The number of patients with a hospital billing for micafungin increased by 30% during the 12-month period ending in August 2015 to approximately 108,000 patients. The vast majority of patients were adults aged 17 years and older who accounted for approximately 96% (104,000 patients), while patients aged 0-16 years accounted for approximately 4% (4,000 patients) of total patients. Among the pediatric patients, approximately 58% (2,300 patients) were aged 2-11 years while 29% (1,147 patients) were aged 12-16 years and 14% (562 patients) were aged 0-1 years.

Table 2.2.1

Nationally Estimated Number of Patients Who Had A Hospital Billing for Micafungin From U.S. Non -Federal Hospital setting, September 2010 through August 2015

	Sept. 2010 - Aug. 2011		Sept. 2011 - Aug. 2012		Sept. 2012 - Aug. 2013		Sept. 2013 - Aug. 2014		Sept. 2014 - Aug. 2015	
	Patient (n)	% Share	Patient (n)	% Share	Patient (n)	% Share	Patient (n)	% Share	Patient (n)	% Share
Micafungin	83,040	100.0%	96,213	100.0%	102,259	100.0%	113,028	100.0%	107,661	100.0%
0 - 16 years	1,825	2.2%	2,277	2.4%	3,222	3.2%	4,528	4.0%	3,954	3.7%
0 -1 years	363	19.9%	523	23.0%	539	16.7%	838	18.5%	562	14.2%
2 - 11 years	960	52.6%	1,220	53.6%	1,882	58.4%	2,675	59.1%	2,300	58.2%
12 - 16 years	529	29.0%	582	25.5%	856	26.6%	1,087	24.0%	1,147	29.0%
17+ years	81,221	97.8%	93,942	97.6%	99,064	96.9%	108,510	96.0%	103,707	96.3%

*Patient age groups are inclusive of all patients up to the day before their next birthday For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months)

**Patient age subtotals may not sum exactly due to patients aging during the study, and may be counted more than once in the individual age categories For this reason, summing across patient age bands is not advisable and will result in overestimates of patient counts

IMS Health, ICHarUS. September 2010 through August 2015. Extracted November 2015. File: 2015-1945 Micafungin BPCA.xlsx

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	19-Jan-2016
Time Period of Search	16-Mar-2005* through 31-Aug-2015
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query (Product-Manufacturer Reporting Summary)
Product Names	Mycamine, Micafungin
Search Parameters	All ages, all outcomes, worldwide

** Initial US Approval Date*

3.1.2 Inclusion Criteria for Pediatric Case Series

For the purposes of this review, DPV included pediatric cases that reported:

- Fatal outcomes, OR
- Serious, unlabeled adverse events

AND

- Did not meet exclusion criteria (see Figure 3.2.2)

All FAERS reports retrieved were analyzed and reviewed. The reports that met the inclusion criteria were included in the case series.

3.2 RESULTS

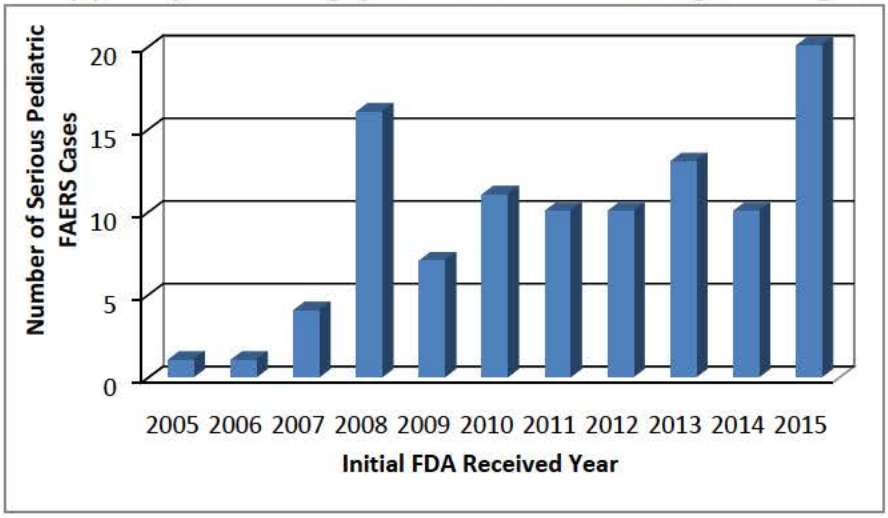
3.2.1 Total number of FAERS cases by Age

Table 3.2.1 Total Adult and Pediatric FAERS Reports from 16-Mar-2005 to 31-Aug-2015 with Micafungin*

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	922 (201)	822 (121)	390 (59)
Pediatrics (0 - <17 years)	108 (19)	**103‡ (14)**	50§ (2)

** May include duplicates and transplacental exposures, and have not been assessed for causality*
† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
‡ See Figure 3.2.2
§ 12 additional cases of pediatric deaths were identified among cases not reporting an age.

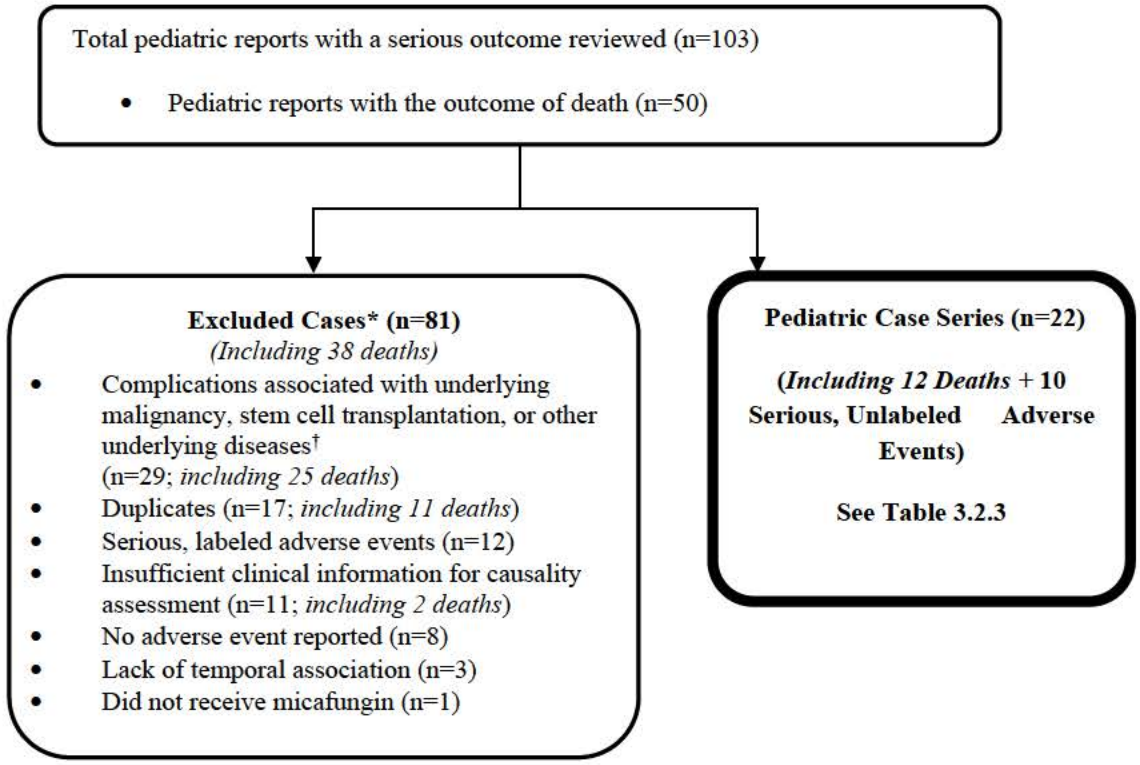
Figure 3.2.1 Serious Pediatric Reports for Micafungin (N=103)
-- by year of FDA receipt from 16-Mar-2005 through 31-Aug-2015



3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 103 pediatric reports with a serious outcome (See Table 3.2.1). See Figure 3.2.2 below for the specific selection of cases to be summarized in Sections 3.3 and 3.4.

Figure 3.2.2 Selection of Serious Pediatric Cases with Micafungin



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

† Cases were excluded if the reported time-to-onset of event was greater than 30 days after micafungin discontinuation

3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with Micafungin (N=22)

Age	0 - < 4 months	7	
	4 months - < 2 years	2	
	2 - < 6 years	3	
	6 - < 12 years	4	
	12 - < 17 years	6	
Sex	Male	10	
	Female	12	
Country	United States	1	
	Foreign	21	*(Japan: 13)*
Initial Reported Indication*	Treatment	13	
	Prophylaxis	8	
	Unknown	1	
Serious Outcome†	Death	12	
	Other serious	12	
	Hospitalized	4	
	Life-threatening	3	

* Initial reported indication- the information that was provided in the indication field of the MedWatch report or case narrative.

† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=12)

We identified 12 fatal pediatric reports with micafungin in the FAERS database from 16-Mar-2005 through 31-Aug-2015. Summary narratives of the fatal cases are below.

FAERS Case # 6345541, Japan Initial FDA Received Date: 28-Jun-2007

Case Notes: Micafungin initiated for the treatment of a suspected fungal infection from 20-Jan-2007 until death on (b) (6).

Preterm female (500 gm) was born on (b) (6) and started on ventilator support. She developed sepsis and was treated with hydrocortisone, ampicillin, amikacin, cefotaxime, fluconazole, and immunoglobulin. On 20-Jan-2007, a fungal infection was suspected and she was started on micafungin 0.5 mg/kg intravenous (IV) twice daily (BID). On (b) (6), she underwent small intestine resection and intestinal fistulization due to necrotizing enterocolitis. On (b) (6) she died of a generalized fungal infection while on micafungin. At the time of death, the micafungin dose had increased from 0.5 to 3 mg/kg IV BID. Pathological findings on autopsy revealed development of *Aspergillus* in different sites of the body.

Reviewer Comments: *This case describes the complicated clinical course of a premature infant with disseminated aspergillosis which did not respond to micafungin. The exact cause of death was not reported; however, death was reportedly associated with disseminated aspergillosis.*

FAERS Case # 6550743, Japan Initial FDA Received Date: 29-Jan-2008

Case Notes: Micafungin initiated for the treatment of candidemia from 31-Jul-2007 to 13-Aug-2007; death occurred on (b) (6)

Preterm male (496 gm) was born on (b) (6) and immediately placed on ventilator support. He was started on ampicillin, amikacin, fluconazole, hydrocortisone, and immunoglobulin. On 31-Jul-2007, the white blood cell count decreased, filgrastim was started, and antibiotics were changed to micafungin, ceftazidime, and arbekacin. Micafungin was started at 1 mg/kg/day for candidemia and eventually increased to 2 mg/kg/day on 09-Aug-2007. Decreased platelet count was reported on 09-Aug-2007 and he was started on platelet concentration infusion. On 14-Aug-2007, he developed tachycardia and then a gradual decrease in heart rate and blood pressure. He died on (b) (6) from cardiac failure, multiorgan failure, intraventricular hemorrhage, disseminated intravascular coagulation, and neonatal asphyxia. The reporting physician commented that drugs were not involved in the cause of death. Autopsy results were not reported.

Reviewer Comments: *This case describes the complicated clinical course of a premature infant. This case lacks clinical details and autopsy findings, which limits our causality assessment. Reported adverse events occurred prior to the initiation of micafungin or were highly confounded by underlying medical conditions and concomitant medications. Death was reportedly associated with cardiac failure, multiorgan failure, and disseminated intravascular coagulation.*

FAERS Case # 6737871, Japan Initial FDA Received Date: 13-Aug-2008

Case Notes: Micafungin initiated for the treatment of possible fungal pneumonia from 09-Apr-2008 until death on (b) (6).

2-year-old female with rhabdomyosarcoma received chemotherapy (carboplatin, etoposide, and irinotecan) from 01-Apr-2008 to 03-Apr-2008 and experienced subsequent bone marrow suppression. On 07-Apr-2008, pulmonary symptoms deteriorated, *Klebsiella* was detected, and pneumonia was diagnosed based on chest x-ray findings. Panipenem/betamipron, amikacin, and fosfluconazole were started on 07-Apr-2008. Micafungin was added on 09-Apr-2008 at a dose of 30 mg daily (3.8 mg/kg/day). Sulfamethoxazole/trimethoprim was administered from 10-Apr-2008 to 12-Apr-2008, and then voriconazole was started on 16-Apr-2008. Her symptoms were not responding and she died on (b) (6) due to aggravation of pneumonia. Autopsy results were not reported.

Reviewer Comments: *This case describes the complicated clinical course of an immunocompromised patient. This case lacks clinical details and autopsy findings, which limits our causality assessment. Reported adverse events either occurred prior to the initiation of micafungin or were associated with underlying malignancy and concomitant medications. Death was reportedly associated with pneumonia unresponsive to multiple antimicrobial agents.*

FAERS Case # 6781172, Japan Initial FDA Received Date: 23-Sep-2008

Case Notes: Micafungin initiated for prophylaxis from 16-May-2008 to 30-May-2008; death occurred on (b) (6).

1-year-old male with medulloblastoma received cyclophosphamide, mesna, cisplatin, vincristine, intramedullary methotrexate, and dexamethasone starting on 07-May-2008. Due to neutropenia, piperacillin and micafungin 10 mg IV daily (1 mg/kg/day) were started on 16-May-2008. Eight days later, C-reactive protein (CRP) increased, pyrexia developed, piperacillin was replaced with cefpirome, and the fever continued (blood culture and beta-D-glucan were negative). On 27-May-2008, cefpirome was replaced with panipenem/betamipron. On 28-May-2008, fever continued, disseminated intravascular coagulation (DIC) developed, dalteparin and clindamycin were started, and micafungin was increased to 50 mg IV daily (5 mg/kg/day). On 30-May-2008, abdominal computed tomography (CT) scan revealed multiple liver abscesses. On 30-May-2008, micafungin, panipenem and clindamycin were discontinued and replaced with liposomal amphotericin B, meropenem, and vancomycin. Pyrexia persisted and beta-D-glucan and blood culture were still negative. On 01-Jun-2008, hemophagocytic syndrome was diagnosed and hemorrhage observed in upper gastrointestinal tract. Aggravation of hemophagocytic syndrome and hemorrhage of the gastrointestinal tract persisted and he died on (b) (6) of hemorrhagic shock. Autopsy revealed gastrointestinal hemorrhage was induced by multiple abscesses of the liver associated with *Penicillium* species.

Reviewer Comments: *This case describes the complicated clinical course of an immunocompromised patient. The reported events were confounded by underlying myelosuppressive drugs, underlying malignancy, gastrointestinal tract hemorrhage, and mycotic liver abscesses. Death was reportedly associated with hemorrhagic shock due to mycotic liver abscesses and occurred eight days after micafungin discontinuation.*

FAERS Case # 6823078, Japan Initial FDA Received Date: 17-Nov-2008

Case Notes: Micafungin initiated for prophylaxis from 19-Apr-2008 to 20-May-2008; death occurred on (b) (6).

9-year-old female with alveolar soft part sarcoma started micafungin 1 mg/kg IV daily prior to allogeneic bone marrow transplant (BMT). On (b) (6) she underwent BMT consisting of fludarabine, melphalan, methotrexate, and total body irradiation (TBI). On an unreported date after BMT, she developed febrile neutropenia, cardiac failure, and graft-versus-host disease (GVHD). On (b) (6), she developed thrombotic microangiopathy and died of a cerebral hemorrhage. Reported concomitant medications included tacrolimus, filgrastim, immunoglobulin, cefozopran, prednisolone, albumin, piperacillin/tazobactam, ceftazidime, dopamine, and furosemide. The reporting pediatrician considered tacrolimus and GVHD as possible causes of thrombotic microangiopathy.

Reviewer Comments: *This case describes the complicated clinical course of an immunocompromised patient. The reported events were confounded by concomitant medications, underlying malignancy, BMT, and GVHD. Death was reportedly associated with a cerebral hemorrhage.*

FAERS Case #6866544, Japan Initial FDA Received Date: 12-Dec-2008

Case Notes: Micafungin initiated for prophylaxis Jan-2008 to Mar-2008, restarted on an unreported date, and then used for treatment at an increased dose from 25-Jul-2008 until death on (b) (6)

5-year-old male with acute lymphoblastic leukemia (ALL) was treated and achieved complete remission. During maintenance treatment (Sep-2007) bone marrow and central relapses were observed and remission

could not be obtained with chemotherapy alone. In (b) (6) he underwent BMT and conditioning with etoposide, melphalan, TBI, and GVHD prophylaxis with tacrolimus and methotrexate. Micafungin (dose not reported) was administered during this time for prophylaxis and was discontinued in Mar-2008. He developed hydrocephalus due to aseptic meningitis with convulsions and consciousness disturbance and a ventriculoperitoneal shunt was placed. Micafungin was resumed at 3 mg/kg/day. On 17-Jun-2008, bone marrow relapse developed and on 20-Jun-2008, chemotherapy (etoposide and cytarabine) was started and continued until 27-Jun-2008. Neutropenia persisted and on an unreported date, bacteremia with *S. epidermidis* occurred. On 17-Jul-2008, pyrexia developed and he was started on meropenem and eventually changed to biapenem on 23-Jul-2008 due to persistent fever. On 25-Jul-2008, fungal infection was suspected and vancomycin and micafungin 100 mg IV daily (6 mg/kg/day) were started along with various other antibacterials over the next few weeks. On 31-Aug-2008, redness was observed on the postauricular area where the ventriculoperitoneal shunt was placed and redness and swelling expanded. The ventriculoperitoneal shunt was removed 05-Sep-2008. A CT scan revealed diffuse low density areas in both lungs and small papules appeared on the skin; herpes simplex virus was suspected and acyclovir was started. On 25-Sep-2008, cough and dyspnea developed, and the blood culture from 25-Sep-2008 was found to be positive for fungus (*Trichosporon asahii*) and beta-d-glucan was positive (58.9 pg/mL; reference range not reported). Micafungin was stopped on 27-Sep-2008 for unspecified reasons and replaced with voriconazole. Dyspnea rapidly progressed and he was prepared for intubation. His consciousness level decreased, rigid convulsion developed, and he died on (b) (6) Autopsy results were not reported.

Reviewer Comments: *This case describes the complicated clinical course of an immunocompromised patient. The reported events were confounded by underlying myelosuppressive drugs, concomitant medications, underlying malignancy, and BMT. Death was reportedly associated with trichosporonosis.*

FAERS Case # 6875375, Japan Initial FDA Received Date: 24-Dec-2008

Case Notes: Micafungin initiated for the treatment of a fungal infection from 05-Sep-2008 to 08-Sep-2008; death occurred on (b) (6) .

14-year-old male was hospitalized for the treatment of recurrent ALL on (b) (6) Subsequently, chemotherapy was administered from 04-Aug-2008 to 15-Aug-2008. On 20-Aug-2008, he was leukopenic with occasional pyrexia of 38°C or higher. A diagnosis of sepsis was made and he was started on meropenem, amikacin, and vancomycin with no improvement in pyrexia. On 25-Aug-2008, filgrastim was started due to no improvement in white blood cell count. On 27-Aug-2008, administration of gabexate mesilate was started due to the development of disseminated intravascular coagulation. On 05-Sep-2008, since pyrexia was persistent and an increased beta-D-glucan was noted, a diagnosis of fungal infection was made and micafungin 150 mg IV daily was started. On 06-Sep-2008, blood *Aspergillus* antigen was positive and a diagnosis of pulmonary aspergillosis was made. Due to no improvement in the fungal infection, micafungin was discontinued on 08-Sep-2008 and liposomal amphotericin B was initiated the following day. On 17-Sep-2008, voriconazole was added and on 23-Sep-2008, solitary ventricular extrasystole was noted. Since there were no particular symptoms, it was judged that no specific treatment was required and serum potassium was 3.4 mEq/L (normal range not reported). On 24-Sep-2008, the patient suffered ventricular tachycardia leading to ventricular fibrillation/torsade de pointes. Resuscitation was performed immediately which aborted the ventricular tachycardia/torsade de pointes. Liposomal amphotericin B and voriconazole were discontinued and the patient was started on propranolol and mexiletine as anti-arrhythmic drugs. Serum potassium was reported to be low (3.0

mEq/L; normal range not reported); thereafter, the patient had ventricular tachycardia repeatedly. On 26-Sep-2008, use of amiodarone led to termination of the ventricular tachycardia with no further recurrence. On 27-Sep-2008, oliguria developed, for which blood purification therapy was performed. Subsequently, the patient's renal function improved but pulmonary aspergillosis worsened. As chemotherapy could not be performed, ALL worsened. On (b) (6), the patient died of ALL aggravation, pulmonary aspergillosis, and respiratory failure. Autopsy results were not reported.

Reviewer Comments: *This case describes the complicated clinical course of an immunocompromised patient. The reported adverse events either occurred prior to or after micafungin, or were confounded by underlying myelosuppressive drugs, underlying hematologic malignancy, hypokalemia, and concomitant medications including liposomal amphotericin B and voriconazole. Death occurred 30 days after micafungin discontinuation and was reportedly associated with worsening ALL, pulmonary aspergillosis, and respiratory failure.*

FAERS Case #7910769, France Initial FDA Received Date: 22-Apr-2011

Case Notes: Micafungin initiated for the treatment of suspected axillary and inguinal lesions suggestive of mycosis from 01-Apr-2011 to 05-Apr-2011; death occurred on (b) (6)

Premature female (850 gm) born at 24 weeks and 3 days of pregnancy. At seven minutes of life, she was intubated and her course of disease was marked by hyaline membrane disease and patent ductus arteriosus. Subsequently, she received two courses of ibuprofen, and surgery was performed on (b) (6) to close ductus arteriosus. On (b) (6), she presented with septic shock requiring fluid administration. She received dopamine until (b) (6), and hydrocortisone and cefotaxime until (b) (6) for an unspecified infection. On (b) (6), micafungin 2 mg IV daily (2.4 mg/kg/day) was started for axillary and inguinal lesions suggestive of mycosis. On (b) (6), after some improvement, she presented with refractory hypoxemia. On (b) (6), refractory hypoxemia continued with bilateral fluffy opacities within the distended lungs, and pulmonary lesions suggestive of bronchopulmonary dysplasia. Ventilation by high frequency oscillation was performed. Nitric oxide was administered in spite of the absence of pulmonary arterial hypertension. Echocardiography revealed hypertrophic obstructive cardiomyopathy without stenosis of aorta, aortic isthmus, and aortic valve. On (b) (6), she was transferred to palliative care and died on (b) (6). Death was considered to be related to hypertrophic obstructive cardiomyopathy. Autopsy was ongoing at the time of the report and results were not reported.

Reviewer Comments: *This case describes the complicated clinical course of a premature infant. The reported adverse event of hypertrophic cardiomyopathy was confounded by underlying medical conditions and concomitant medications. The exact cause of death was not reported; however, death was reportedly associated with hypertrophic obstructive cardiomyopathy.*

FAERS Case # 8536074, France Initial FDA Received Date: 30-Apr-2012

Case Notes: Micafungin initiated for the treatment of invasive candidiasis from 11-Jan-2012 until death on (b) (6)

2-month-old female with mediastinal rhabdoid tumor was started on etoposide and carboplatin. She developed neutropenia and was initiated on lenograstim. On 09-Jan-2012, blood culture was positive from two central catheters and on the following day, a second central catheter was introduced. On 11-Jan-2012, she started micafungin 2 mg/kg daily. On 19-Jan-2012, due to lack of efficacy, micafungin was increased to 4 mg/kg daily. On an unspecified date, liposomal amphotericin B was started due to persistent lack of

efficacy with micafungin. On an unspecified date, liposomal amphotericin B was eventually discontinued and micafungin was increased to 10 mg/kg daily and then to 12 mg/kg daily due to lack of efficacy. She developed skin rash on an unspecified date, thrombocytopenia from 28-Dec-2011 to 04-Mar-2012, and renal insufficiency from 08-Jan-2012 to 04-Mar-2012. Concomitant medications included sulfamethoxazole/trimethoprim from 26-Dec-2011 to 03-Mar-2012, and midazolam/sufentanyl from 25-Dec-2011 to 03-Mar-2012 for sedation. On (b) (6), she died due to multi-organ failure. The reporter specified that there was a presence of fungemia despite combination antifungal therapy and no particular adverse events were related to micafungin. Autopsy results and susceptibility testing of the *Candida* spp. were not reported.

Reviewer Comments: *This case lacks clinical details and autopsy findings, which limits our causality assessment. The exact cause of death was not reported; however, death was reportedly associated with multi-organ failure in a patient with invasive candidiasis not controlled with dose-escalation of micafungin or the combination of micafungin with liposomal amphotericin B.*

FAERS Case # 10017824, Japan Initial FDA Received Date: 18-Mar-2014

Literature Report: Kadoi E, Shinoda K, Toyoshima Y, et al. A case of disseminated aspergillosis after stem cell transplantation. Jpn J of Pediatr Hematol Oncol. 2014;51:524-8.

Case Notes: Micafungin initiated for prophylaxis, and then for treatment at a later date.

13-year-old female with atypical chronic myelogenous leukemia (CML) presented with a relapse approximately one year after BMT. Re-induction was performed with fludarabine, cytosine, arabinoside, idarubicin, and filgrastim. BMT was performed again in the second remission phase with TBI, fludarabine, melphalan, anti-thymocyte globulin (ATG), and GVHD prophylaxis with tacrolimus and methotrexate. Since a part of the ward was under construction, micafungin 1.5 mg/kg IV daily and weekly monitoring of beta-D-glucan and *Aspergillus* antigen were performed once weekly. On day 111 post-BMT, she developed fever and cough, and a CT scan revealed mild infiltrative shadows. She developed GVHD and was initiated on methylprednisolone. On day 145, beta-D-glucan was 116 pg/mL (reference range not reported) and *Aspergillus* antigen was positive for the first time with a value of 4.6 (units and reference range not reported). Suspecting invasive aspergillosis, micafungin was switched to voriconazole. Gastrointestinal GVHD was then treated with oral beclomethasone solution and enteric-coated capsules while methylprednisolone was tapered off. On day 172, a CT scan showed diffuse and multiple occurrences of galaxy signs, nodular shadow, and consolidation in the lung field. Micafungin was restarted at an increased dose of 6 mg/kg IV daily. On day 211, a general CT scan showed multiple abscesses in the skull, and shadows suspected to be abscesses in both the thyroid and kidney. This was considered to be angiogenic dissemination of fungal abscesses and the voriconazole dose was increased with the aid of therapeutic drug monitoring. On day 217, liposomal amphotericin B was added to micafungin and voriconazole. On day 229, disseminated aspergillosis was difficult to control and she experienced cerebral ventricular rupture of a brain abscess with bleeding and died on day 237. No autopsy was performed.

Reviewer Comments: *This case describes the complicated clinical course of an immunocompromised patient. The reported events were confounded by underlying myelosuppressive drugs, concomitant medications, underlying hematologic malignancy, and BMT. Death was reportedly associated with invasive aspergillosis which developed while on micafungin prophylaxis and did not respond to treatment with the combination of micafungin, voriconazole, and liposomal amphotericin B.*

FAERS Case # 10345064, Italy Initial FDA Received Date: 28-Jul-2014

Case Notes: Micafungin initiated for prophylaxis from 16-Jun-2014 to 07-Jul-2014; death occurred on (b) (6).

10-year-old female was diagnosed with ALL on 05-Jul-2013 and treated with induction chemotherapy and blinatumomab. Reported concomitant medications included piperacillin/tazobactam, levofloxacin, metronidazole, acyclovir, dexamethasone, omeprazole, meropenem, and sulfamethoxazole/trimethoprim. Micafungin 90 mg daily (2 mg/kg/day) was initiated on 16-Jun-2014 for prophylaxis. During the aplasia phase of her chemotherapy, despite multiple antimicrobials, she developed high fevers and the presence of diffuse septic emboli in her arms and trunk. Blood cultures on 06-Jul-2014 were positive for *Candida guillermondii* and *Sporopachidermia lactativora* while on micafungin prophylaxis. Micafungin was discontinued and she was started on liposomal amphotericin B and voriconazole. Sepsis worsened and she developed progressive pulmonary failure and died on (b) (6) due to cardiocirculatory arrest.

Reviewer Comments: *This case describes the complicated clinical course of an immunocompromised patient. Fungemia with two organisms developed while on micafungin prophylaxis. Death occurred seven days after micafungin discontinuation and was reportedly associated with fungemia, sepsis, progressive pulmonary failure, and eventually cardiocirculatory arrest.*

FAERS Case #10834795, France Initial FDA Received Date: 19-Feb-2015

Case Notes: Micafungin initiated for the treatment of invasive candidiasis on 29-Jan-2015; death occurred on either (b) (6) or (b) (6).

Premature female born on (b) (6). No other medical history was reported and the only concomitant medication reported was voriconazole. On 29-Jan-2015, she was started on micafungin 2 mg/kg IV daily for invasive candidiasis. On 04-Feb-2015, the micafungin dose was increased to 4 mg/kg IV daily. On 09-Feb-2015, micafungin was further increased to 8 mg/kg IV daily and voriconazole was added. Later on 09-Feb-2015, her clinical condition worsened and she died on either (b) (6) or (b) (6). Autopsy results were not reported. The reporting pharmacist thought death was due to the patient's prematurity.

Reviewer Comments: *This case describes the complicated clinical course of a premature infant. This case lacks clinical details and autopsy findings, which limits our causality assessment. The exact cause of death was not reported; however, death was reportedly associated with prematurity.*

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS UNLABELED ADVERSE EVENT CASES (N=10)

In addition to the fatal cases, 10 cases with serious outcomes and unlabeled adverse events were also selected for inclusion into the case series. The following unlabeled adverse events were reported once each: cheilitis, conjunctivitis, cytokine storm, decreased hemoglobin, hematemesis, hepatic calcification, hypertension, hypertriglyceridemia, hypokalemia, increased amylase, increased creatine phosphokinase, increased lactate dehydrogenase, leukocytosis, myoclonus, neonatal cholestasis, seizure, systemic inflammatory response syndrome, thirst, urinary sediment abnormal, and veno-occlusive disease. Case descriptions for these 10 cases are found in Appendix C (Table C2).

Overall, these cases were highly confounded or of poor quality and did not provide relevant information, such as time to onset or outcome of the adverse event, to establish the relationship between the adverse events and micafungin. No specific pattern of adverse events was noted. The reported adverse events may be due to underlying disease processes, concurrent disease states and medications, or other coincidental factors. However, a role played by micafungin cannot be excluded.

4 DISCUSSION

Pediatric patients aged 0-16 accounted for approximately 2-4% of the total patients over the examined time; approximately 4,000 pediatric patients had a hospital billing for micafungin from non-federal hospital inpatient and outpatient ER settings in the 12-month period ending in August 2015. Findings from this review should be interpreted in the context of the known limitations of the databases used, see Appendix A for description and limitations of the databases. The analysis of sales distribution data showed the majority of micafungin bottles/packages were distributed to non-retail inpatient setting. We focused our analysis on the inpatient setting only; therefore, these estimates may not apply to other settings of care in which these products are used such as outpatient or mail/specialty pharmacy settings. The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time. All changes over time should be considered approximate and may be due to random error.

With interest in identifying rare, serious, or unlabeled events associated with micafungin use in the pediatric population, we focused our FAERS analysis on the pediatric cases with serious outcomes. Our analysis resulted in 22 cases for our case series. Of these, 12 cases reported a fatal outcome and 10 cases cited non-fatal outcomes that were associated with serious, unlabeled adverse events.

No new safety signals were identified in this review. Limitations to case interpretation included incomplete case descriptions, underlying disease processes, concurrent disease states or medications, or other coincidental factors.

In general, the fatal cases described highly immunocompromised patients with complicated clinical courses. Deaths were primarily associated with invasive fungal disease (n=7), prematurity (n=3), complications post-BMT (n=1), or pneumonia (n=1). The temporally associated adverse events may be due to underlying disease processes, concurrent disease states and medications, or other coincidental factors. However, a role played by micafungin cannot be excluded. In addition, the reported adverse events were consistent with the risks known in the labeling for micafungin; no increased severity was observed in these reports.

The cases of non-fatal outcomes that were associated with serious, unlabeled adverse events were highly confounded or of poor quality and did not provide relevant information, such as time to onset or outcome of the adverse event, to establish the relationship between the adverse events and micafungin. No specific pattern of adverse events was noted.

5 CONCLUSION

Overall, there were no patterns or trends in drug utilization or in the FAERS cases series to suggest a new safety signal was associated with micafungin. The FAERS cases were either of poor quality or highly confounded making it difficult to assess a causal relationship between micafungin and the reported adverse events. The reported adverse events are likely due to underlying disease processes, concurrent disease states or medications, or other coincidental factors. However, a contributory role played by micafungin could not be excluded.

In summary, the reported adverse events were consistent in nature with the risks cited in the micafungin product label; no increased severity was observed in these reports. There is no evidence from these data to suggest that there are new pediatric safety concerns with micafungin at this time.

6 RECOMMENDATIONS

DPV does not recommend any labeling changes at this time. DPV will continue routine monitoring of the adverse event reports associated with the use of micafungin.

7 REFERENCES

1. Development Resources for Mycamine® (micafungin), Medical, Statistical, and Clinical Pharmacology Reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Safety and Innovation Act of 2012 (FDASIA). Available at: http://www fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm316937 htm. Accessed: January 2016.

2. Mycamine® (micafungin), NDA 021506 – Approved Product Label. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021506s015lbl.pdf Accessed: January 2016.

3. IMS Health, National Sales Perspectives™ Data Extracted November 2015. File: DATA 2015-1945 Micafungin BPCA.xlsx

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Inpatient HealthCare Utilization System (IHCarUS)

The IMS, Inpatient HealthCare Utilization System (IHCarUS) provides hospital inpatient and outpatient encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from 2002, is collected weekly and monthly and is available 25-30 days after the end of each monthly period. This robust data set includes >670 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include 13.6 million patients and 49.6 million visits per year projected to approximately 37 million inpatient visits and 550 million outpatient (including Emergency Department) visits per year, representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. IMS'

datasets are geographically representative, and include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

The IMS Hospital CDM sample does not include Federal hospitals and some other specialty hospitals (including children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the IMS CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IMS' Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IMS' patient level data to be representative and accurate across multiple therapeutic areas.

8.2 APPENDIX B FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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 or not 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.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH MICAFUNGIN (N=22)

TABLE C1. FATAL PEDIATRIC CASES (N=12)	
FAERS Case # - Version #	**Manufacturer Control #**
6345541-2	2007JP002539
6550743-3	2008JP000133
6737871-3	2008JP003670
6781172-5	2008JP004313
6823078-1	2008JP003087
6866544-6	2008JP005661
6875375-5	2008US003462
7910769-1 *Duplicate 8515525-1*	FR-SANOFI-AVENTIS-2011SA023860 *FR-SANOFI-AVENTIS-2012SA024240*
8536074-1	FR-ASTELLAS-2012EU001298
10017824-2	JP-ASTELLAS-2014JP002174
10345064-4	ITASTELLAS-2014EU010180
10834795-1 *Duplicate 10871856-2*	FR-ASTELLAS-2015US005045 *FR-ASTELLAS-2015US005240*

TABLE C2. UNLABELED, SERIOUS PEDIATRIC CASES (N=10)

FAERS Case# - Version#	Initial FDA Received Date	Manufacturer #	Country	Underlying Medical Condition	Reported MedDRA Preferred Terms
6816873-2	**12-Nov-2008**	**2008JP004621**	**Japan**	**Leukemia (ALL)**	Alanine aminotransferase increased, Aspartate aminotransferase increased, Bacterial infection, Cytokine storm, Hypertension

Case Notes: Micafungin 50 mg IV QD initiated for prophylaxis on 11-Jan-2008 to 25-Jan-2008 (50 mg = 1.25 mg/kg based on reported weight of 40 kg)
9-year-old male with ALL underwent HSCT on (b) (6) with a conditioning regimen of melphalan, etoposide, fludarabine, methotrexate, and GVHD prophylaxis with methotrexate and tacrolimus. Micafungin 50 mg IV QD was initiated on 11-Jan-2008, prior to HSCT. On 17-Jan-2008, hypertension developed with blood pressure of 134/86 mmHg and he was treated with nicardipine and recovered from the event on 22-Jan-2008 with a blood pressure of 98/58 mmHg. On 21-Jan-2008, ALT and AST increased to 85 and 55 IU/L, respectively (normal ranges not reported). On 24-Jan-2008, a bacterial infection was treated with vancomycin. On 25-Jan-2008, micafungin was discontinued and he developed hypercytokinemia that was treated with methylprednisolone and resolved on 02-Feb-2008. Micafungin was replaced with itraconazole on an unspecified date. On 15-Feb-2008, ALT and AST normalized at 43 IU/L and 16 IU/L, respectively without symptomatic treatment.
Reviewer Comments: *Based on the temporal association, a causal relationship between micafungin and the unlabeled events of cytokine storm and hypertension cannot be excluded. The reported events were confounded by myelosuppressive chemotherapy, underlying hematologic malignancy, and concomitant medications including methotrexate and tacrolimus. The reported hepatic adverse events (alanine aminotransferase increased and aspartate aminotransferase increased) are consistent with micafungin labeling.*

6992650-1	**04-May-2009**	**2009US001253**	**Great Britain**	**Cardiac Surgery**	Rash erythematous, Systemic inflammatory response syndrome

Case Notes: Micafungin (dose, frequency and route not reported) initiated for the treatment of candidiasis.
2-year-old female underwent elective cardiac surgery on (b) (6) and developed a subsequent infection with *Candida parapsilosis*. She was initially treated with liposomal amphotericin B, and then micafungin was added. On the first day of micafungin treatment, she developed systemic inflammatory response syndrome and an erythematous rash. Micafungin was discontinued and liposomal amphotericin B was continued for 21 days. The outcomes of these events were not reported.
Reviewer Comments: *Limited case details precluded a meaningful causality assessment. Based on the temporal association, a causal relationship between micafungin and the unlabeled event of systemic inflammatory response syndrome cannot be excluded. The reported events were confounded by recent surgery, ongoing Candida infection, and concomitant administration with liposomal amphotericin B. The reported event of rash is consistent with micafungin labeling.*

7048341-2	**31-Jul-2008**	**2008JP003119**	**Japan**	**Leukemia**	Acute graft versus host disease in skin, Alanine aminotransferase increased, Aspartate aminotransferase increased, Engraftment syndrome, Hypertriglyceridaemia, Liver disorder, Renal disorder, Urinary sediment abnormal

Case Notes: Micafungin 3 mg/kg IV daily initiated on 16-Sep-2007.
13-year-old female with acute biphenotypic leukemia initiated micafungin 16-Sep-2007 and underwent a cord blood stem cell transplant on (b) (6). The conditioning regimen included fludarabine, cyclophosphamide, and TBI. On day 17, she experienced pyrexia, joint pain, increased white blood cell count, and was later diagnosed with engraftment syndrome (onset considered 04-Oct-2007). At the same time, hepatic function tests were elevated with an AST of 141 IU/L and ALT 204 IU/L (normal ranges not reported). On 07-Oct-2007, the dose of micafungin was increased to 6 mg/kg/day and cefozopran was replaced by vancomycin and panipenem/betamipron. On 08-Oct-2007, methylprednisolone was started for the engraftment syndrome with resolution on 10-Oct-2007. On 10-Oct-2007, hypertriglyceridemia was observed and no treatment was provided; renal disorder (urinary sediment abnormal) also developed and resolved on 21-Dec-2007. On 16-Oct-2007, the dose of micafungin returned to 3 mg/kg/day and the following medications were discontinued: methylprednisolone, vancomycin, and panipenem/betamipron. On 22-Oct-2007, petechial erythema appeared on the neck, limbs and soles and skin GVHD was diagnosed and treated with increased doses of tacrolimus with resolution. On 14-Nov-2007, micafungin was discontinued, and as of 08-Jul-2008, liver disorder was resolving but hypertriglyceridemia did not resolve.
Reviewer Comments: *The reported events of acute GVHD in skin and engraftment syndrome are expected complications in patients with hematologic malignancies post-HSCT. Based on the temporal association, a causal relationship between micafungin and the unlabeled events of hypertriglyceridemia and urinary sediment abnormal cannot be excluded. The reported events were confounded by myelosuppressive chemotherapy, underlying hematologic malignancy, and concomitant medications including tacrolimus, methylprednisolone, vancomycin, and panipenem/betamipron. The reported adverse events alanine aminotransferase increased, aspartate aminotransferase increased, liver disorder, and renal disorder are consistent with micafungin labeling.*

7064631-5	**16-Jul-2009**	**2009US002675**	**Japan**	**Myelodysplastic Syndrome**	Acute graft versus host disease in skin, Seizure, Hypernatraemia, Blood alkaline phosphatase increased, Liver function test abnormal, Alanine aminotransferase increased, Thirst, Blood creatine phosphokinase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Brain abscess, Hypokalaemia
Case Notes: Micafungin 50 mg IV QD initiated on 31-May-2009 for prophylaxis; micafungin dose subsequently increased to 150 mg IV QD from 09-Jun-2009 to 27-Jun-2009 for treatment of brain abscess. 15-year-old male with myelodysplastic syndrome initiated tacrolimus on 19-May-2009 for GVHD prophylaxis and underwent BMT on (b) (6) On 31-May-2009, micafungin was initiated for presumed prophylaxis (50 mg IV QD). On 08-Jun-2009, he developed a general seizure which was suspected to be drug-induced and tacrolimus was discontinued. Seizures were initially treated with diazepam and then phenytoin. The same day, an emergent CT scan and MRI scan of the head revealed hemorrhagic infarction and cerebral abscess; therefore, he was initiated on liposomal amphotericin B and the micafungin dose was increased to 150 mg IV QD. On 16-Jun-2009, hypernatremia was observed, fructose-added glycerol was suspected and changed to mannitol. On 22-Jun-2009, he experienced increased creatine phosphokinase (4,800 mg/dL; normal range not reported), hypokalemia (1.9 mEq/L; normal range not reported) and abnormal liver function tests (AST, ALT, ALP, and GGT were elevated). No symptoms of muscle pain were observed with the elevated CPK and a CK isoenzyme test revealed the elevated CPK was not originating from the brain or cardiac muscle. Potassium supplementation was administered with correction of potassium level. On 23-Jun-2009, liposomal amphotericin B was discontinued. On 25-Jun-2009, he developed thirst due to mannitol and therapy was changed to fructose-added glycerol, and he experienced biopsy-confirmed skin GVHD. Hypokalemia resolved on 26-Jun-2009 and micafungin was discontinued on 27-Jun-2009. The increased CPK resolved on 03-Jul-2009. The outcomes of hypernatremia, abnormal liver function tests, and brain abscess were not reported. Concomitant medications included granisetron, famotidine, acyclovir, cefpirome, phenytoin, metoclopramide, edaravone, tacrolimus, ceftazidime, vancomycin, and diazepam. ***Reviewer Comments:*** *The reported events of skin GVHD and engraftment syndrome are expected complications in patients with hematologic disease post-BMT. Based on the temporal association, a causal relationship between micafungin and the unlabeled events of seizure, thirst, increased CPK, brain abscess, and hypokalemia cannot be excluded. The reported events were confounded by BMT, underlying hematologic disease, and concomitant medications including mannitol, fructose-added glycerol, tacrolimus, methylprednisolone, vancomycin, and panipenem/betamipron. The reported hepatic adverse events are consistent with micafungin labeling.*					
7846531-1 ***dup7501691-1***	**10-Feb-2011**	**TRP_07540_2011** ***2010US002625***	**USA**	**Systemic Lupus Erythematosus**	Haematemesis, Haemoglobin decreased, Refusal of treatment by relative, White blood cell count increased
Literature Report: Shenoi S, Emery HM. Successful treatment of invasive gastric mucormycosis in a child with systemic lupus erythematosus. Lupus. 2010;19:646-9. ***Case Notes:*** Micafungin (dose, frequency and route not reported) initiated for treatment of peritonitis and sepsis, and then for treatment of gastric mucormycosis using a dose of 3.5 mg/kg/day. 14-year-old male with SLE received monthly pulse cyclophosphamide, weekly pulse methylprednisolone, oral prednisolone (1 mg/kg twice daily), and hydroxychloroquine. After the third weekly dose of pulse methylprednisolone, he was admitted to the hospital with non-bilious emesis, severe abdominal pain, guarding, and signs of septic shock. He was started on mechanical ventilation, dopamine, epinephrine, vasopressin, piperacillin/tazobactam, gentamicin, vancomycin, and micafungin for suspected peritonitis and sepsis. CT scan showed diffuse free fluid and emergency exploratory laparotomy drained 600 mL of pus, no bowel perforations were noted and external gastric mucosa appeared normal. On the third day of hospitalization, he developed pulmonary hemorrhage with worsening hypoxia and laboratory studies suggested early macrophage activation syndrome thought secondary to a lupus flare. He was started on three days of high-dose IV methylprednisolone (1.5 mg/kg every 8 hours) and IV tacrolimus. On hospital day 13, he developed abdominal cramping and was noted to have an increasing CRP and repeat abdominal CT scan showed no new abscess formation. EGD was performed and showed multiple serpiginous, purplish, nodular submucosal lesions of the gastric wall. Biopsy revealed large, irregular, branching hyphae with paucity of septae suggestive of invasive mucormycosis. Gastric brushings revealed *Candida glabrata* and fungal PCR detected *Rhizopus microsporus*. Liposomal amphotericin B (5 mg/kg/day) and micafungin (3.5 mg/kg/day) were started and his immunosuppressive medications were tapered over subsequent days. On hospital day 18, he experienced massive hematemesis managed supportively since the family refused any surgical intervention such as gastrectomy. He had further hematemesis but was managed medically with pantoprazole, micafungin, and liposomal amphotericin B. He completed 6 months of IV antifungal therapy and will then receive 12 months of oral posaconazole. ***Reviewer Comments:*** *The reported unlabeled events were confounded by underlying SLE, peritonitis, sepsis, gastric mucormycosis, and concomitant medications including liposomal amphotericin B, tacrolimus, and methylprednisolone.*					
8011374-1	**27-Jun-2011**	**JP-ASTRAZENECA-2011SE14835**	**Japan**	**Leukemia (ALL)**	Myoclonus
Case Notes: Micafungin 300 mg IV (frequency not reported) initiated for the treatment of pneumonia from 06-Jan-2011 to 13-Jan-2011.					

15-year-old male with ALL received consolidation therapy including pirarubicin, vincristine, 6-mercaptopurine, prednisolone, and L-asparaginase on 21-Dec-2010. On 28-Dec-2010, he developed abdominal pain and vomiting. On 31-Dec-2010, he was diagnosed with severe acute pancreatitis and was started on artificial respiration and continuous hemodiafiltration. On 05-Jan -2011, meropenem, teicoplanin, and micafungin were started for pneumonia. On 07-Jan-2011, he developed myoclonus around the lips and gradually developed all over the body and was treated with clonazepam. Omeprazole and teicoplanin were discontinued on 12-Jan-2011, and micafungin was discontinued on 13-Jan-2011. Other concomitant medications discontinued around this time were ulinastatin and Neo-Minophagen C on 12-Jan-2011. On 16-Jan-2011, he recovered from myoclonus.

Reviewer Comments: *Based on the temporal association, a causal relationship between micafungin and the unlabeled event of myoclonus cannot be excluded. The reported positive dechallenge was confounded by the discontinuation of four other medications around the same time as micafungin.*

8270278-2	**01-Dec-2011**	**BR-ASTELLAS-2011US007948**	**Brazil**	**Preterm Birth**	Neonatal cholestasis, Off label use, Overdose

Case Notes: Micafungin 4 – 7 mg/kg IV (frequency not reported) initiated for an unspecified *Candida tropicalis* infection from 10-Oct-2011 to 04-Nov-2011.

Preterm female with hepatosplenomegaly and hepatic carcinoma was initiated on Micafungin on 10-Oct-2011. During micafungin therapy, she experienced neonatal cholestasis. She recovered from cholestasis on 04-Nov-2011 when micafungin was discontinued. Concomitant medications were not reported.

Reviewer Comments: *This case lacks clinical details which limits our causality assessment. Based on the temporal association, a causal relationship between micafungin and the unlabeled event of neonatal cholestasis cannot be excluded. The reported event is confounded by the underlying medical conditions of preterm birth, hepatosplenamegaly, and hepatic carcinoma.*

9515587-2	**11-Sep-2013**	**FR-ASTELLAS-2013EU007701**	**France**	**Preterm Birth**	Overdose, Hepatic calcification

Case Notes: Micafungin 5 mg/kg IV QD initiated for treatment of peritonitis and sepsis from 13-Jun-2013 to 05-Aug-2013.

Preterm female born on (b) (6) at 26 weeks. Neonatal antiretroviral prophylaxis was instituted with zidovudine and maintained for 30 days without any noteworthy adverse effects. From (b) (6), blood cultures revealed systemic candidiasis due to *Candida albicans*. Micafungin was initiated on (b) (6) (at 10 days of life), and by (b) (6), the fungal blood cultures were negative. Coagulase-negative staphylococci were also listed as a causative organism for peritonitis and sepsis. On (b) (6), an ultrasound discovered hepatic nodules (calcified lesions) in segments five and six of the liver, which did not appear to be candidiasis lesions. Radiological monitoring of the lesions was instituted with abdominal ultrasounds on (b) (6); the ultrasounds showed subsequent regression of the lesions. Micafungin was discontinued on (b) (6) and she did not receive any corrective treatment for the hepatic calcifications and was discharged on (b) (6). Concomitant medications included dopamine (b) (6)), ibuprofen (b) (6)), insulin (b) (6)), pantoprazole (dates not reported), paracetamol (dates not reported), vancomycin ((b) (6)), gentamicin (dates not reported), meropenem ((b) (6)), and zidovudine ((b) (6)).

Reviewer Comments: *This case lacks clinical details which limits our causality assessment. Based on the temporal association, a causal relationship between micafungin and the unlabeled event of hepatic calcification cannot be excluded. The reported event of hepatic calcification is confounded by the underlying medical conditions of preterm birth, peritonitis, and sepsis with two organisms (C. albicans and coagulase-negative staphylococci), and multiple concomitant medications.*

10436110-2	**08-Sep-2014**	**JP-SHIONOGI, INC-2014000857**	**Japan**	**Leukemia (ALL)**	Amylase increased, Blood lactate dehydrogenase increased, Cheilitis, Conjunctivitis, Hepatic function abnormal, Urticaria

Case Notes: Micafungin 150 mg IV QD initiated for febrile neutropenia on 10-Jul-2014 to 14-Jul-2014.

10-year-old male received chemotherapy on an unreported date. On 11-Jul-2014, urticaria appeared during a platelet transfusion and it resolved on the same day with chlorpheniramine. Also on 11-Jul-2014, the event of herpes cheilitis appeared and was treated with acyclovir until 15-Jul-2014. On 12-Jul-2014, a platelet transfusion was performed and on the same day, he developed conjunctivitis and was treated with levofloxacin until 14-Jul-2014. On 14-Jul-2014, his amylase increased to 1064 U/L (normal range: 42-114 U/L) from a baseline of 44 U/L. Micafungin and levofloxacin were discontinued on 14-Jul-2014. The event of abnormal hepatic function was treated with monoammonium glycyrrhizinate/glycine/aminoacetic acid/DL-methionine from 17-Jul-2014 to 18-Jul-2014. No treatment was given for the events of increased LDH and increased amylase. On 15-Jul-2014, the event of herpes cheilitis resolved. On 30-Jul-2014, the event of increased amylase resolved. As of 15-Aug-2014, the event of abnormal hepatic function resolved and the event of increased LDH was improving. The reporting physician commented the event of increased LDH was considered to be associated with hematopoietic recovery after chemotherapy. Concomitant medications included acetaminophen (09-Jul-2014 to 12-Jul-2014), acyclovir (11-Jul-2014 to 15-Jul-2014), doripenem (09-Jul-2014 to 16-Jul-2014), cefpirome (07-Jul-2014 to 09-Jul-2014), and teicoplanin (08-Jul-2014 to 14-Jul-2014). Reported relevant medical history included ALL, febrile neutropenia, anemia, enterocolitis, hypokalemia, hypogammaglobulinemia, hyponatremia, sepsis, thrombocytopenia, and upper respiratory tract infection inflammation.

Reviewer Comments: *This case lacks clinical details which limits our causality assessment. Based on the temporal association, a causal relationship between micafungin and the unlabeled events of increased*

amylase, cheilitis, and conjunctivitis cannot be excluded. The reported events were confounded by receipt of chemotherapy, hematologic malignancy, and concomitant medications. The reported hepatic adverse events and urticaria are consistent with micafungin labeling.					
10971826-1	**31-Mar-2015**	**ES-BAXTER-2015BAX015485**	**Spain**	**Not Reported Required HSCT**	Cytomegalovirus test positive, Venoocclusive liver disease
Case Notes: Micafungin 22 mg IV QD initiated for prophylaxis on 01-Apr-2014 (22 mg = 2 mg/kg based on a reported weight of 11 kg). 10-month-old male underwent allogeneic peripheral HSCT with a conditioning regimen consisting of busulfan, cyclophosphamide, and mesna. From 23-Mar-2014 to 03-Apr-2014, he received seven days of IV phenytoin for busulfan seizure prophylaxis. Busulfan was administered from 25-Mar-2014 to 28-Mar-2014. From 24-Mar-2014 to 01-Apr-2014, he received sulfamethoxazole/trimethoprim for an empiric indication. On 01-Apr-2014, he received acyclovir, micafungin, and metronidazole for an empiric indication or prophylaxis. On an unreported date, the patient was positive for CMV. On an unreported date, an abdominal ultrasound showed mild hepatosplenomegaly with homogeneous echogenicity, permeable suprahepatic, diameter of the portal was 6.3 mm with hepatopetal flow of 16.4 cm/s, and no free intraperitoneal liquid. The rest of the explorations were without significant findings. On (b) (6) the patient experienced a life threatening event of mild VOD, which caused or prolonged hospitalization. Micafungin, acyclovir, and metronidazole were maintained during the event of VOD. As of 25-Apr-2014, the patient was recovering from VOD. ***Reviewer Comments:*** *Based on the temporal association, a causal relationship between micafungin and the unlabeled event of VOD cannot be excluded. The reported events were confounded by underlying or concurrent conditions (HSCT), receipt of chemotherapy, and concomitant medications including busulfan (labeled for hepatic VOD).*					

Abbreviations: ALL, acute lymphoblastic leukemia; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMT, bone marrow transplant; CK, creatine kinase; CMV, cytomegalovirus; CPK, creatine phosphokinase; CRP, C-reactive protein; CT, computerized tomography; EGD, esophagogastroduodenoscopy; GGT, gamma-glutamyl transferase; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; IV, intravenous; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; QD, once daily; SLE, systemic lupus erythematosus; TBI, total body irradiation; VOD, veno-occlusive disease

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIMOTHY J JANCEL
02/26/2016

JUSTIN A MATHEW
02/26/2016

RAJDEEP K GILL
02/26/2016
Drug use data in this review has been cleared by drug use data vendors.

KELLY Y CAO
02/26/2016

GRACE CHAI
02/26/2016

STEVEN C JONES
02/26/2016