Pediatric Focused Safety Review: Mycamine (micafungin)

Pediatric Advisory Committee Meeting

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Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information: Mycamine (micafungin)

- **Therapeutic Category:** echinocandin
- **Sponsor:** Astellas Pharma, Inc.
- **Indication:** In adults and pediatric patients 4 months and older:
  - Treatment of Patients with Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses
  - Treatment of Patients with Esophageal Candidiasis
  - Prophylaxis of *Candida* Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT)

Background Drug Information: Mycamine (micafungin)

- **Formulation:** 50 mg and 100 mg single-use vials
- **Dosage and Administration:** intravenous infusion

Indication	Dose		
	Adult	**Pediatric 30 kg or less**	**Pediatric greater than 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 HSCT Recipients	50 mg daily	1 mg/kg/day (maximum 50 mg daily)	

Background Drug Information: Mycamine (micafungin)

- **Original Market approval:** March 16, 2005
- **Pediatric labeling changes:** June 21, 2013
  - Approval for all indications extended to include pediatric patients down to 4 months of age.

Pediatric Efficacy and Safety Study: Mycamine (micafungin)

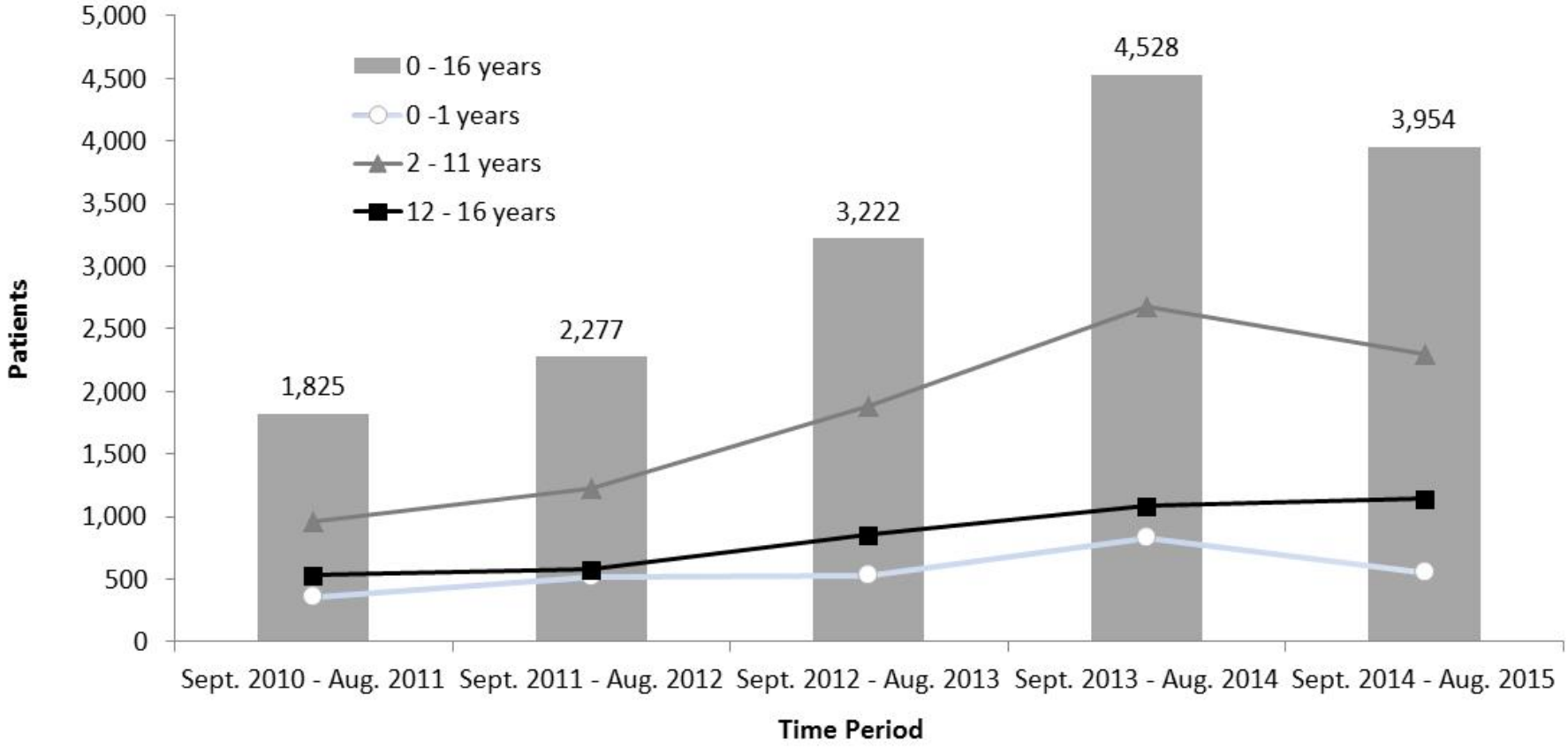
- Efficacy was extrapolated from adequate and well controlled trials in adult patients for all approved indications, and supported by pediatric pharmacokinetic (PK) and safety data.
  - PK data in 229 patients 4 months - 16 years of age were characterized using population PK analyses.
  - Two randomized, double-blind, active control studies investigated the safety and efficacy of Mycamine in both adult and pediatric patients for:
    - Treatment of invasive candidiasis and candidemia
    - Prophylaxis of Candida infections in patients undergoing HSCT
  - The safety of Mycamine was assessed in 479 patients (3 days-16 years of age) who received at least one dose (0.75 mg/kg -10 mg/kg) in 11 separate studies.
    - The most frequent treatment emergent adverse reactions with Mycamine were vomiting (31%), diarrhea (22%) and pyrexia (22%).

Pediatric Labeling Changes: Mycamine (micafungin)

- **8.4 Use in Specific Populations, Pediatric Use**
  - Safety and effectiveness of Mycamine in pediatric patients 4 months of age 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 younger than 4 months of age have not been established.
- Additional pediatric information on population PK, dosing, adverse reactions and clinical trials included throughout labeling.

Pediatric Drug Utilization: Mycamine® (micafungin)[1]

Nationally Estimated Number of Pediatric Patients (0-16 years) Who Had A Hospital Billing for Micafungin From U.S. Non-Federal Inpatient and Outpatient ER Hospital settings, September 2010 through August 2015



[1]*Source: IMS Health, IHCarUS. September 2010 through August 2015. Extracted November 2015.*

Total Number* of Mycamine Adverse Event Reports Since Original Approval (March 16, 2005- August 31, 2015)

	All reports (US)	Serious (US)**	Death (US)
Adults (≥ 17 yrs.)	922 (201)	822 (121)	390 (59)
Pediatrics (0-<17 yrs.)	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 events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

†12 additional cases of pediatric deaths were identified among cases not reporting an age.

Selection of Serious Pediatric FAERS Cases

Total pediatric reports with a serious outcome reviewed (n=103)

- Pediatric reports with the outcome of death (n=50)

Excluded Cases (n=81)

(Including 38 deaths)

- Complications associated with underlying malignancy, stem cell transplantation, or other underlying diseases† (n=29; *25 deaths*)
- Duplicates (n=17; *11 deaths*)
- Serious, labeled adverse events (n=12)
- Insufficient clinical information for causality assessment† (n=11; *2 deaths*)
- No adverse event reported (n=8)
- Lack of temporal association (n=3)
- Did not receive micafungin (n=1)

Pediatric Case Series (n=22)

(*Including 12 Deaths and 10 Serious, Unlabeled Adverse Events*)

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

Summary of Serious Adverse Events (n=22): Mycamine (micafungin)

- Fatal Adverse Events (n=12)
- Nonfatal Unlabeled Adverse Events (n=10)*
  - Veno-occlusive disease
  - Hypertension
  - Hypertriglyceridemia
  - Hypokalemia
  - Hematemesis
  - Decreased hemoglobin
  - Leukocytosis
  - Abnormal urinary sediment
  - Elevated creatine phosphokinase
  - Thirst
  - Hepatic calcification
  - Neonatal cholestasis
  - Increased amylase
  - Increased lactate dehydrogenase
  - Conjunctivitis
  - Cheilitis
  - Seizure
  - Myoclonus
  - Cytokine storm
  - Systemic inflammatory response syndrome

* Each case may include multiple unlabeled adverse events

**Unlabeled events are underlined.

Fatal Adverse Events (n=12): Mycamine (micafungin)

- Age range: birth – 14 years of age (5 preterm neonates).
- Highly immunocompromised patients with complicated clinical courses.
- Associated conditions: invasive fungal disease (n=7), prematurity (n=3),complications post-bone marrow transplant (n=1), or pneumonia (n=1).
- Concomitant medications: various immunosuppressive agents, antibiotics and corticosteroids.
- Most adverse events were due to underlying disease processes, concurrent disease states and medications, or other coincidental factors; no reasonable basis to conclude causality.
- Many of the reported adverse events were closely related to labeled events.

Serious Non-Fatal Unlabeled Adverse Events (n=10): Mycamine (micafungin)

- Age range: 10 days- 15 years of age.
- Highly immunocompromised patients with complicated courses.
- Associated conditions: Leukemia (n=4), Preterm birth (n=2), HSCT (n=3)*, Cardiac surgery (n=1), Hepatic carcinoma (n=1), Systemic Lupus Erythematosus (n=1), Myelodysplastic syndrome and bone marrow transplant (n=1).
- Concomitant medications: various immunosuppressive agents, antibiotics and corticosteroids.
- Cases highly confounded (e.g., underlying disease processes) or of poor quality and did not provide relevant information (e.g., 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.

* 3 patients with Leukemia also had HSCT

Summary Pediatric Focused Safety Review: Mycamine (micafungin)

- This concludes the pediatric focused safety review.
- Mycamine is approved in patients 4 months of age and older.
- Overall the cases were highly confounded or had limited information to assess causality.
- The safety review identified no new safety signals.
- FDA recommends continuing ongoing surveillance.
- Does the Committee concur?

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