

**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 Review

Date: February 25, 2019

Safety Evaluator: Timothy Jancel, PharmD, MHS, BCPS-AQ ID, BCIDP
Division of Pharmacovigilance II

Medical Officer: Ivone Kim, MD, FAAP
Division of Pharmacovigilance I

Team Leader: Kelly Cao, PharmD
Division of Pharmacovigilance II

Deputy Division Director: Ida-Lina Diak, PharmD, MS
Division of Pharmacovigilance II

Product Names: Cubicin® and Cubicin® RF (daptomycin for injection)

Pediatric Labeling Approval Dates: March 29, 2017: Complicated skin and skin structure infections
September 1, 2017: *Staphylococcus aureus* bacteremia

Application Type/Number: NDA 021572, Multiple ANDAs

Sponsor: Merck Sharp & Dohme Corp., multiple others

OSE RCM #: 2018-2673

TABLE OF CONTENTS

Executive Summary	1
1 Introduction	2
1.1 Pediatric Regulatory History	2
1.2 Relevant Labeled Safety Information	5
2 Methods and Materials	6
2.1 FAERS Search Strategy	6
3 Results	7
3.1 FAERS	7
3.1.1 Total Number of FAERS Reports by Age	7
3.1.2 Selection of Serious Pediatric Cases in FAERS	7
3.1.3 Characteristics of Pediatric Cases	9
3.1.4 Summary of Fatal Pediatric Cases (N=0)	9
3.1.5 Summary of Non-Fatal Pediatric Serious Cases (N=6)	9
4 Discussion	12
5 Conclusion	13
6 Recommendation	13
7 References	14
8 Appendices	15
8.1 Appendix A. FDA Adverse Event Reporting System	15
8.2 Appendix B. FAERS Line Listing of the Daptomycin Pediatric Case Series (N=6)	16

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cubicin® (daptomycin for injection) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with daptomycin in pediatric patients.

The FDA approved daptomycin on September 12, 2003 and it is currently indicated for complicated skin and skin structure infections (cSSSI) in adult and pediatric patients (1 to 17 years of age), *Staphylococcus aureus* bacteremia in pediatric patients (1 to 17 years of age), and *S. aureus* bacteremia in adult patients, including those with right-sided infective endocarditis. This review was prompted by pediatric labeling approved on March 29, 2017 that expanded the indication from adults to pediatric patients 1 to 17 years of age for the treatment of cSSSI. On September 1, 2017, additional pediatric labeling was approved that expanded the indication from adults to pediatric patients 1 to 17 years of age for the treatment of *S. aureus* bacteremia.

Of the pediatric reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly attributable to daptomycin. Of the 6 serious and unlabeled adverse event cases in pediatric patients less than 18 years of age, no specific pattern of adverse events was noted. Four cases were confounded by underlying conditions or concomitant medications and lacked sufficient information for a meaningful causality assessment. Two cases described infusion-related adverse events associated with a voluntary nationwide recall involving eight lots of Hospira, Inc.'s daptomycin in 2018.

DPV did not identify any pediatric safety concerns for daptomycin and recommends no regulatory action at this time.

DPV will continue to monitor all adverse events associated with the use of daptomycin.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cubicin® (daptomycin for injection) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA).^{1,2} This review focuses on serious unlabeled adverse events associated with daptomycin in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Daptomycin is a cyclic lipopeptide class of antibacterials available for intravenous (IV) use.^{3,4} The FDA initially approved daptomycin on September 12, 2003 for the treatment of complicated skin and skin structure infections (cSSSI) in adult patients caused by susceptible Gram-positive organisms.⁵ On May 25, 2006, daptomycin was approved for the treatment of *Staphylococcus aureus* bacteremia in adult patients, including those with right-sided endocarditis, caused by methicillin-susceptible and methicillin-resistant strains. Daptomycin is not indicated for the treatment of pneumonia or for the treatment of left-sided infective endocarditis due to *S. aureus*.³

This review was prompted by pediatric labeling approved on March 29, 2017 that expanded the indication from adults to pediatric patients 1 to 17 years of age for the treatment of cSSSI.⁶ On September 1, 2017, additional pediatric labeling was approved that expanded the indication from adults to pediatric patients 1 to 17 years of age for the treatment of *S. aureus* bacteremia.⁷ For both pediatric indications, daptomycin is not recommended in patients younger than one year of age.³

Daptomycin is supplied in single-dose vials, each containing 500 mg daptomycin as a sterile, lyophilized powder. There are two formulations of daptomycin, Cubicin® and Cubicin® RF, that have differences regarding storage and reconstitution; it is recommended to carefully follow the reconstitution and storage procedures in labeling. In pediatric patients, daptomycin is infused over a 30- or 60-minute period based on age; unlike in adults, daptomycin should not be administered over a 2-minute period.^{3,4}

The daptomycin pediatric dosage and administration is based on indication and age group and is described in Tables 1 and 2.³

Table 1. Recommended Dosage Regimen for Pediatric Patients (1 to 17 Years of Age) with Complicated Skin and Skin Structure Infections, Based on Age

Age Group	Dosage*	Duration of Therapy
12 to 17 years	5 mg/kg once every 24 hours infused over 30 minutes	Up to 14 days
7 to 11 years	7 mg/kg once every 24 hours infused over 30 minutes	
2 to 6 years	9 mg/kg once every 24 hours infused over 60 minutes	
1 to less than 2 years	10 mg/kg once every 24 hours infused over 60 minutes	

* Recommended dosage is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.

Table 2. Recommended Dosage Regimen for Pediatric Patients (1 to 17 Years of Age) with *S. aureus* Bacteremia, Based on Age

Age Group	Dosage*	Duration of Therapy
12 to 17 years	7 mg/kg once every 24 hours infused over 30 minutes	Up to 42 days
7 to 11 years	9 mg/kg once every 24 hours infused over 30 minutes	
1 to 6 years	12 mg/kg once every 24 hours infused over 60 minutes	

* Recommended dosage is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.

The safety and effectiveness of daptomycin for the treatment of cSSSI and *S. aureus* bacteremia have been established in pediatric patients 1 to 17 years of age. The use of daptomycin in these age groups was supported by evidence from adequate and well-controlled studies in adults, with additional data from pharmacokinetic studies in pediatric patients, and from safety, efficacy and pharmacokinetic studies in pediatric patients with cSSSI and *S. aureus* bloodstream infections.^{6,7} The two pediatric clinical studies that were primarily used for the cSSSI and *S. aureus* bacteremia indications are summarized below.

Daptomycin Indication:**cSSSI**

Study Identifier: DAP-PEDS-07-03

ClinicalTrials.gov Identifier: NCT00711802⁸

Literature Reference: Bradley et al.⁹

This was a randomized, multicenter study in pediatric patients 1 to 17 years of age with cSSSI caused by Gram-positive pathogens. The primary objective was to evaluate daptomycin safety and the secondary objective was to assess daptomycin efficacy compared to standard-of-care (SOC) comparator agents; the study was not powered to compare safety or efficacy end points between treatment arms. Patients with known bacteremia, osteomyelitis, endocarditis, and pneumonia at baseline were excluded. Patients were randomized 2:1 to receive daptomycin or SOC, which included IV therapy with either vancomycin, clindamycin, or an anti-staphylococcal semisynthetic penicillin. Patients could switch to oral therapy after clinical improvement was demonstrated. The different age groups and daptomycin doses evaluated were as follows:

adolescents (12 to 17 years) treated with 5 mg/kg, children (7 to 11 years) treated with 7 mg/kg, children (2 to 6 years) treated with 9 mg/kg, and infants (1 to <2 years) treated with 10 mg/kg. The intent-to-treat population consisted of 257 patients randomized to the daptomycin group and 132 patients randomized to SOC. Approximately 95% of patients switched to oral therapy; the mean day of switch was day 4, and ranged from day 1 to day 14. The clinical success rates determined at 7 to 14 days after last dose of therapy (test-of-cure visit) were 88.3% for daptomycin and 86.4% for SOC. The safety analysis of daptomycin included 256 pediatric patients (1 to 17 years of age) treated with daptomycin and 133 patients treated with SOC. Daptomycin was discontinued in 2.7% of patients due to an adverse reaction, while SOC was discontinued in 5.3% of patients. The most common adverse events were diarrhea (7.0% daptomycin, 5.3% SOC) and increased blood creatine phosphokinase (5.5% daptomycin, 5.3% SOC). The safety profile in the clinical trial of cSSSI pediatric patients was similar to that observed in the cSSSI adult patients and the FDA Clinical Review concluded that there were no additional significant adverse reactions to daptomycin or new safety concerns from those described in the current product label evident in this pediatric clinical trial.⁶

Daptomycin Indication:

Bacteremia caused by *S. aureus*

Study Identifier:

DAP-PEDBAC-11-02

ClinicalTrials.gov Identifier:

NCT01728376¹⁰

Literature Reference:

Arrieta et al.¹¹

This was a randomized, multicenter study in pediatric patients 1 to 17 years of age with bacteremia caused by either proven or probable *S. aureus*. The primary objective was to evaluate daptomycin safety and the secondary objectives included comparing daptomycin efficacy with SOC and pharmacokinetic analysis; the study was not powered to compare safety or efficacy endpoints between treatment arms. Patients were randomized 2:1 to daptomycin or SOC over a period of up to 42 days. SOC included IV therapy with either vancomycin, cefazolin, or an anti-staphylococcal semisynthetic penicillin. Daptomycin dosing was guided through pharmacokinetic studies with target steady state exposure levels in children that were comparable to adults treated with 6 mg/kg; using these metrics, dosing was designated as 12 mg/kg (1 to 6 years of age), 9 mg/kg (7 to 11 years of age), and 7 mg/kg (12 to 17 years of age). No patients 1 to <2 years of age were enrolled. Most of the patients in both treatment groups had methicillin-susceptible *S. aureus* (MSSA) bacteremia (80.0% in daptomycin, 73.1% in SOC) followed by methicillin-resistant *S. aureus* (MRSA) bacteremia (12.7% in daptomycin, 11.5% in SOC). The study indicated that pediatric patients 1 year of age and older demonstrated similar efficacy of daptomycin-treated subjects to those receiving SOC (88.2% and 77.3% in the microbiologic modified intent-to-treat population, respectively) for the treatment of *S. aureus* bacteremia. The safety analysis included 81 patients who received at least 1 dose of study medication; 55 patients received daptomycin and 26 patients received SOC. Daptomycin was discontinued in 5.5% of patients due to an adverse reaction, while SOC was discontinued in 7.7% of patients. The most common adverse events were vomiting (10.9% daptomycin, 7.7%

SOC) and increased creatine phosphokinase (CPK; 7.3% daptomycin, 0% SOC). The FDA Clinical Review concluded that the safety profile of daptomycin in pediatric patients is similar to what has been seen in the adult clinical trials and in postmarketing reports as well as postmarketing experience with pediatric patients with Gram-positive cSSSI. No new safety signals were apparent from the review of the safety database focusing on CPK, hepatic function, and peripheral neuropathy.⁷

Daptomycin has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The daptomycin labeling includes the following information under Highlights of Prescribing Information. For further daptomycin labeling information, including dosage and administration in adult patients, refer to the full prescribing information.³

-----CONTRAINDICATIONS-----

- Known hypersensitivity to daptomycin (4)

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

- Anaphylaxis/hypersensitivity reactions (including life-threatening): Discontinue CUBICIN and treat signs/symptoms. (5.1)
- Myopathy and rhabdomyolysis: Monitor CPK levels and follow muscle pain or weakness; if elevated CPK or myopathy occurs, consider discontinuation of CUBICIN. (5.2)
- Eosinophilic pneumonia: Discontinue CUBICIN and consider treatment with systemic steroids. (5.3)
- Peripheral neuropathy: Monitor for neuropathy and consider discontinuation. (5.4)
- Potential nervous system and/or muscular system effects in pediatric patients younger than 12 months: Avoid use of CUBICIN in this age group. (5.5)
- *Clostridium difficile*–associated diarrhea: Evaluate patients if diarrhea occurs. (5.6)
- Persisting or relapsing *S. aureus* bacteremia/endocarditis: Perform susceptibility testing and rule out sequestered foci of infection. (5.7)
- Decreased efficacy was observed in adult patients with moderate baseline renal impairment. (5.8)

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

- Adult cSSSI Patients: The most common adverse reactions that occurred in $\geq 2\%$ of adult cSSSI patients receiving CUBICIN 4 mg/kg were diarrhea, headache, dizziness, rash, abnormal liver function tests, elevated creatine phosphokinase (CPK), urinary tract infections, hypotension, and dyspnea. (6.1)
- Pediatric cSSSI Patients: The most common adverse reactions that occurred in $\geq 2\%$ of pediatric patients receiving CUBICIN were diarrhea, vomiting, abdominal pain, pruritus, pyrexia, elevated CPK, and headache. (6.1)
- Adult *S. aureus* bacteremia/endocarditis Patients: The most common adverse reactions that occurred in $\geq 5\%$ of *S. aureus* bacteremia/endocarditis patients receiving CUBICIN 6 mg/kg were sepsis, bacteremia, abdominal pain, chest pain, edema, pharyngolaryngeal pain, pruritus, increased sweating, insomnia, elevated CPK, and hypertension. (6.1)
- Pediatric *S. aureus* bacteremia Patients: The most common adverse reactions that occurred in $\geq 5\%$ of pediatric patients receiving CUBICIN were vomiting and elevated CPK. (6.1)

The daptomycin labeling also includes the following under section 8 USE IN SPECIFIC POPULATIONS, 8.4 *Pediatric Use*:

The safety and effectiveness of CUBICIN in the treatment of cSSSI and *S. aureus* bloodstream infections (bacteremia) have been established in the age groups 1 to 17 years of age. Use of CUBICIN in these age groups is supported by evidence from adequate and well-controlled studies in adults, with additional data from pharmacokinetic studies in pediatric patients, and from safety, efficacy and PK studies in pediatric patients with cSSSI and *S. aureus* bloodstream infections [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].

Safety and effectiveness in pediatric patients below the age of one year have not been established. Avoid use of CUBICIN in pediatric patients younger than one year of age due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs [see Warnings and Precautions (5.5) and Nonclinical Toxicology (13.2)].

CUBICIN is not indicated in pediatric patients with renal impairment because dosage has not been established in these patients.

CUBICIN has not been studied in pediatric patients with other bacterial infections.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 3.

Table 3. FAERS Search Strategy*	
Date of Search	January 2, 2019
Time Period of Search	September 12, 2003 [†] through December 31, 2018
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query, Product-Manufacturer Reporting Summary
Product Terms	Product Active Ingredient: Daptomycin
MedDRA Search Terms (Version 21.1)	All terms
Search Parameters	Age <18 years, all outcomes, worldwide

* See Appendix A for a description of the FAERS database.
† U.S. Approval date

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 4 presents the number of adult and pediatric FAERS reports from September 12, 2003 through December 31, 2018 with daptomycin.

Table 4. Total Adult and Pediatric FAERS Reports* Received by FDA from September 12, 2003 through December 31, 2018 with Daptomycin

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (\geq 18 years)	3,839 (2,160)	3,372 (1,702)	724 (290)
Pediatrics (0 - $<$ 18 years)	92 (54)	79 ^{‡§} (45)	27 ^{‡§} (16)

* 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, and other serious important medical events.
‡ See Figure 1
§ Eight reports of pediatric deaths were identified among reports not reporting an age and were added to the pediatric serious and death report counts

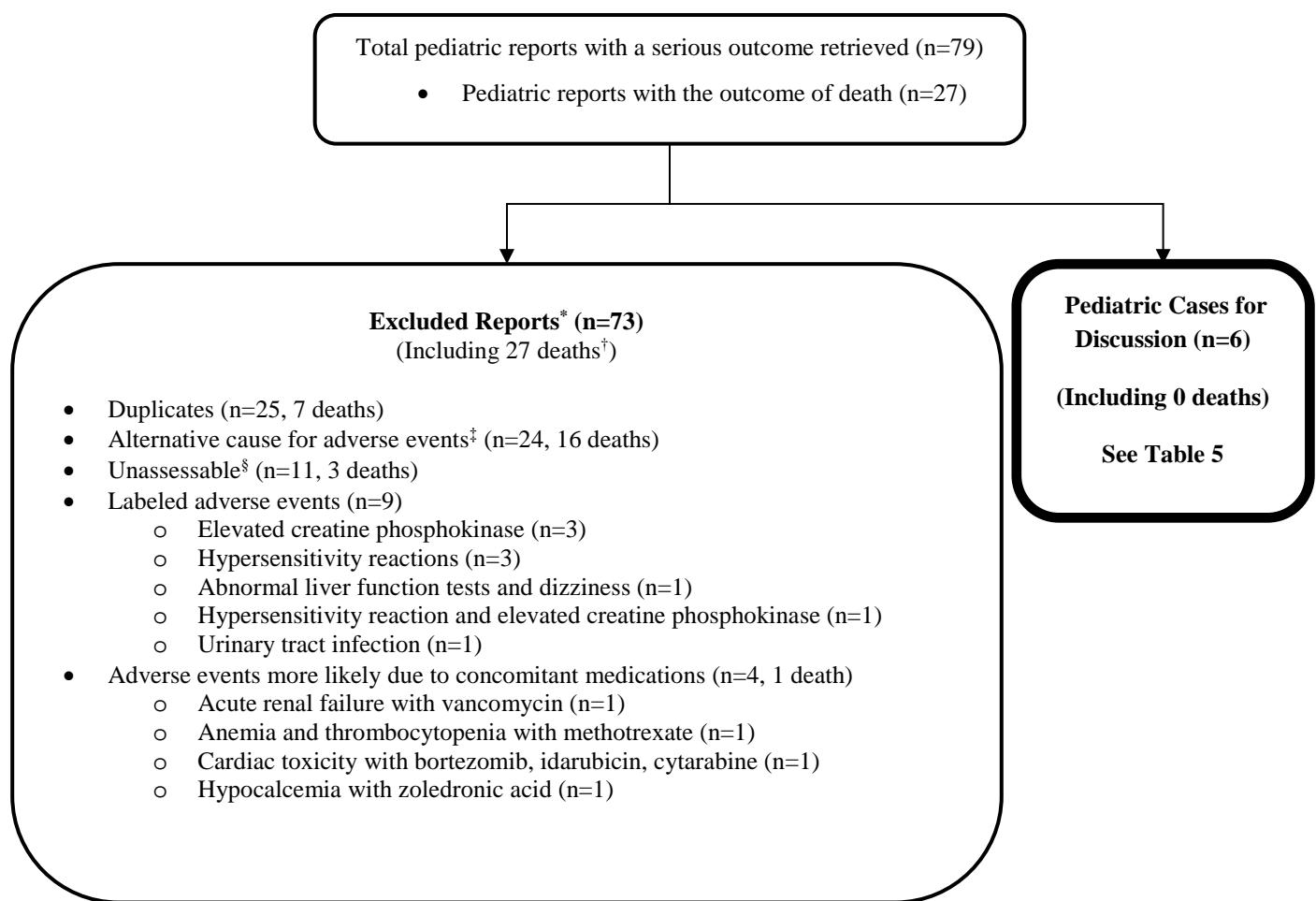
3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 79 pediatric reports with a serious outcome from September 12, 2003 through December 31, 2018.

We reviewed all FAERS pediatric reports; however, our primary focus was on pediatric reports with a serious outcome. We did not identify any new safety concerns among the non-serious pediatric reports. We excluded reports from the case series for various reasons, such as if the adverse event was unlikely to be causally related to the use of daptomycin (e.g., the report was confounded by co-morbid diseases or concomitant medications). We summarize the remaining cases in the sections below.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Daptomycin



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above

† The 27 reports resulting in death were excluded because they were duplicates (n=7), described treatment failure, development of resistance, worsening of congenital disease, or underlying disease progression (n=16; e.g., bacteremia, endocarditis, sepsis, congenital disorders, and hematologic malignancies), contained limited case details for adequate assessment (n=3), or associated with death from cardiomyopathy after receiving multiple drugs labeled for cardiac toxicities (bortezomib, idarubicin, and cytarabine) (n=1)

‡ Indication related, treatment failure, development of resistance, underlying disease progression

§ Case 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) or the information is contradictory, or information provided in the case cannot be supplemented or verified

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the six pediatric cases.

Table 5 summarizes the 6 FAERS cases in pediatric patients with daptomycin reporting a serious outcome received by FDA from September 12, 2003 through December 31, 2018.

Table 5. Characteristics of the FAERS Serious Pediatric Cases with Daptomycin Received by FDA from September 12, 2003 through December 31, 2018 (N=6)		
Age	0 - <1 year	2
	1 - <12 years	3
	12 - <18 years	1
Sex	Male	3
	Female	3
Country	United States	3
	Foreign	3
Serious Outcome [*]	Hospitalization	3
	Other Serious	5

^{*} For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A case may have more than one serious outcome.

3.1.4 Summary of Fatal Pediatric Cases (N=0)

We did not include any fatal pediatric adverse event cases in our case series.

3.1.5 Summary of Non-Fatal Pediatric Serious Cases (N=6)

We identified six FAERS cases with daptomycin in the pediatric population reporting a non-fatal serious outcome. The cases are summarized and organized by MedDRA System Organ Class.

3.1.5.1 Hepatic and Hepatobiliary Disorders (n=3)

Although daptomycin is labeled for abnormal liver function tests, increased alanine aminotransferase, and increased aspartate aminotransferase in section 6 ADVERSE REACTIONS, it is not labeled for cholestasis, increased bilirubin, acute hepatitis, or acute liver injury.³ All three cases contained insufficient information to adequately assess causality and were confounded by underlying medical conditions, concomitant medications, or parenteral nutrition.

Cholestasis (n=1)

FAERS Case Number: 8404776

A literature case report¹² describes a female infant born at 29 weeks (triplet pregnancy) with a clinical course complicated by respiratory distress syndrome and necrotizing enterocolitis. The patient was treated with daptomycin for refractory sepsis caused by vancomycin-resistant *Enterococcus faecium*; daptomycin was started at 6 mg/kg every 12 hours and eventually increased to 15 mg/kg every 12 hours. Daptomycin was administered to the patient for a total of 7 weeks; however, “during this time”, it was reported the patient experienced an increase in liver transaminases (aspartate aminotransferase [AST] 367 IU/mL, alanine aminotransferase [ALT] 187 IU/mL), total bilirubin 10.8 mg/dL, direct bilirubin 5.6 mg/dL, and gamma-glutamyl transpeptidase (GGT) 226 IU/mL; the dates of the laboratory values and normal ranges were not reported. The authors stated the increased laboratory values were suggestive of cholestasis and were attributed to the severity of sepsis and receipt of prolonged parenteral nutrition.

Reviewer’s Comment: The case describes a possible temporal association with daptomycin and the development of increased AST, ALT, bilirubin, and GGT; however, the case contained insufficient information to adequately assess causality such as concomitant medications. In addition, the case was confounded by sepsis and parenteral nutrition, which are possible risk factors for the development of cholestasis in preterm infants.¹³ Daptomycin is not indicated in pediatric patients less than one year of age or for the treatment of enterococcal sepsis.³

Hepatitis and Liver Injury (n=2)

FAERS Case Number: 11566095

An 11-year-old female received daptomycin (“5 mg, once a day”) for the treatment of acute hematogenous osteomyelitis of the femur and septic arthritis of the hip. On the same day daptomycin was started, AST was 34 IU/L (normal high value: 34 IU/L) and ALT was 30 IU/L (normal high value: 55 IU/L). Daptomycin was discontinued two days later for an unspecified reason. One day after the discontinuation of daptomycin, AST and ALT were 64 IU/L and 54 IU/L, respectively. Two days after the discontinuation of daptomycin, it was reported the patient developed “hepatic injury” with an increase in AST and ALT to 558 IU/L and 305 IU/L, respectively. On an unspecified date, the patient was hospitalized and “underwent liver function tests and abdominal or hepatobiliary ultrasound and was diagnosed with reactive hepatitis.” On an unspecified date, it was reported that the patient had a complete recovery. Concomitant medications included acetaminophen and unspecified nonsteroidal anti-inflammatory drugs (NSAIDs).

Reviewer’s Comment: The case describes a possible temporal association with daptomycin and the development of elevations in AST and ALT; however, the case contained insufficient information to adequately assess causality such as past medical history. Hepatic injury was reported 2 days after the discontinuation of daptomycin; the mean half-life of daptomycin in

pediatric patients 7 to 11 years of age is reported to be 6.8 hours³, which makes daptomycin-associated hepatic injury less likely. The case was confounded by concomitant medications labeled for elevations in liver enzymes and severe hepatic reactions, including acetaminophen and NSAIDs.^{14,15} Daptomycin is not indicated for the treatment of osteomyelitis or septic arthritis.³

FAERS Case Number: 13021118

A 4-month-old male with congenital cardiomyopathy received imipenem and daptomycin (“32 mcg daily”) for sepsis. The next day, the patient was diagnosed with “serious acute hepatitis” and AST and ALT were 5,700 and 1,604, respectively (units and normal range not reported). Imipenem and daptomycin were discontinued, and at the time of the report, the patient had not yet recovered.

Reviewer's Comment: This case describes a temporal association with daptomycin and the development of acute hepatitis; however, the case lacked information to adequately assess causality such as underlying medical conditions, concomitant medications, dechallenge results, and results of baseline or follow-up laboratory values. Imipenem is labeled for increased AST, increased ALT, and hepatitis (including fulminant hepatitis).¹⁶ Daptomycin is not indicated in pediatric patients less than one year of age.³

3.1.5.2 Nervous System Disorders (n=1)

Seizure (n=1)

FAERS Case Number: 8730416

A 7-year-old male received daptomycin (4 mg/kg daily) for the treatment of an abscess involving the right great toe. The patient was at the hospital receiving outpatient wound care and after receiving the third dose of daptomycin, the patient had a seizure and was admitted for observation. The reporting physician did not assess the seizure as related to daptomycin because the patient had an unspecified “cardiac history.” The patient had an electroencephalogram (EEG) performed; however, the results were not reported. The patient was discharged and recovered.

Reviewer's Comment: This case describes a temporal association with daptomycin and the development of seizure; however, the case lacked information to adequately assess causality such as concomitant medications, results of the EEG or laboratory tests, and past medical history including details of the patient's cardiac history.

3.1.5.3 General Disorders and Administration Site Conditions (n=2)

The following two cases were associated with a voluntary nationwide recall of daptomycin that reported infusion-related reactions in adult and pediatric patients. Eight lot numbers of Hospira, Inc.’s daptomycin, including lot number 792103A, were associated with adverse event reports

indicative of infusion-related reactions which included labeled and non-labeled events such as chills, tremor, pyrexia, dyspnea, tachycardia, and blood pressure changes.¹⁷ The FDA's Office of Pharmaceutical Quality (OPQ) opened a Tracked Safety Issue (TSI) and Hospira performed an investigation regarding daptomycin infusion-related reactions. The Hospira product that caused the adverse reactions in patients was recalled from the marketplace, new production stopped, and already manufactured lots were withdrawn from distribution. The TSI opened by OPQ was closed in November 2018.

FAERS Case Number: 14403410

A 7-year-old male with sickle cell disease received daptomycin (156 mg daily [8 mg/kg]; Hospira, lot number 792103A) and ceftriaxone (1.5 gm) for sickle cell crisis. On the same day, the patient experienced seizure/convulsions, chills, and severe shaking. While in the hospital, the patient was switched to another manufacturer of daptomycin (non-Hospira) on an unknown date and it was reported the patient did not experience any events. Four days after initially starting daptomycin, the patient was again administered Hospira daptomycin (lot number 792103A) and experienced chills and headache, which were treated with ibuprofen. Daptomycin was discontinued and the outcome of the events was not reported.

Reviewer's Comment: This case describes a temporal association with Hospira daptomycin and the development of infusion-related reactions and a positive rechallenge with Hospira daptomycin; however, the patient did not experience similar adverse events when administered non-Hospira daptomycin.

FAERS Case Number: 14683358 (duplicate FAERS Case Number: 14689724)

A 17-year-old female received daptomycin (400 mg [6 mg/kg]; Hospira, lot number 792103A) for a postoperative infection involving the knee after anterior cruciate ligament repair. After receiving one dose of daptomycin, the patient experienced severe chills, rigors, and heart rate of 120 (normal range not reported). The patient was taken to the hospital by ambulance and was subsequently admitted. Daptomycin was discontinued after the first dose and the patient completely recovered. The patient had no medical conditions and concomitant medications included ibuprofen, acetaminophen, heparin (flush), aspirin, pantoprazole, and piperacillin-tazobactam). Allergies included peanuts, tree nut allergy and pollen.

Reviewer's Comment: This case describes a temporal association with Hospira daptomycin and the development of infusion-related reactions.

4 DISCUSSION

Of the 79 reports reviewed with a serious outcome in pediatric patients less than 18 years of age, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly attributed to daptomycin. Most of the reports had limited information which precluded a meaningful causality assessment, described adverse events that were likely due to comorbidities or concomitant medications (e.g., bacteremia,

endocarditis, sepsis, and hematologic malignancies), were consistent with the known adverse events described in labeling (e.g., hypersensitivity reactions, and increased CPK), or were associated with alternative causes (e.g., indication related, treatment failure, and development of resistance).

Of the 6 serious and unlabeled adverse event cases in pediatric patients less than 18 years of age, no specific pattern of adverse events was noted. Four cases were confounded by underlying conditions or concomitant medications and lacked sufficient information for a meaningful causality assessment. Two cases described infusion-related adverse events associated with a voluntary nationwide recall involving eight lots of Hospira daptomycin in 2018.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for daptomycin at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time, and will continue to monitor all adverse events associated with the use of daptomycin.

7 REFERENCES

1. U.S. Food & Drug Administration, New Pediatric Labeling Information Database. Available at: <https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>. Accessed: January 2, 2019.
2. Development Resources for 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 2, 2019.
3. Cubicin® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; December 2018. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021572s061lbl.pdf. Accessed: January 3, 2019).
4. Cubicin® RF [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; September 2017. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021572s060lblcubicinRF.pdf. Accessed: January 3, 2019).
5. Nambiar S, Thompson S. Clinical Review NDA 21572. Cubicin (daptomycin for injection). September 2003. (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-572_Cubicin.cfm. Accessed: January 7, 2019).
6. Purandare A. Clinical Review NDA 021572. Cubicin (daptomycin for injection). March 2017. (<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM552588.pdf>. Accessed: January 7, 2019).
7. Rister N. Clinical Review NDA 021572. Cubicin (daptomycin for injection). August 2017. (<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM580267.pdf>. Accessed: January 7, 2019).
8. Safety and Efficacy Study of Daptomycin in Pediatric Participants (1 to 17 years-old) With Skin and Skin Structure Infections. (2018). Retrieved from <https://clinicaltrials.gov/ct2/show/NCT00711802> (Identification No. NCT00711802).
9. Bradley J, Glasser C, Patino H, et al. Daptomycin for Complicated Skin Infections: A Randomized Trial. *Pediatrics*. 2017;139(3):e20162477.
10. Safety & Efficacy of Daptomycin Versus Standard of Care (SOC) in 1 - 17 Year Olds With *Staphylococcus Aureus* Bacteremia (MK-3009-005). (2018). Retrieved from <https://clinicaltrials.gov/ct2/show/NCT01728376> (Identification No. NCT01728376).
11. Arrieta AC, Bradley JS, Popejoy MW, et al. Randomized Multicenter Study Comparing Safety and Efficacy of Daptomycin Versus Standard-of-care in Pediatric Patients With Staphylococcal Bacteremia. *Pediatr Infect Dis J*. 2018;37:893-900.
12. Antachopoulos C, Iosifidis E, Sarafidis K, et al. Serum levels of daptomycin in pediatric patients. *Infection*. 2012;40:367-71.
13. Satrom K, Gourley G. Cholestasis in Preterm Infants. *Clin Perinatol*. 2016;43:355-73.
14. Acetaminophen [package insert]. Lake Zurich, IL: Fresenius Kabi USA; October 2015. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204767s000lbl.pdf. Accessed: January 8, 2019).
15. Ibuprofen [package insert]. Shreveport, LA: Dr. Reddy's Laboratories; October 17, 2016. (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=24731405-219c-79b4-ecf0-7d5fbfd94ba>. Accessed January 8, 2019).
16. Primaxin® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; December 2018. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/050587s081lbl.pdf. Accessed: January 8, 2019).
17. FDA Recalls, Market Withdrawals, & Safety Alerts. Hospira Issues Voluntary Nationwide Recall of Daptomycin for Injection Lyophilized Powder for Solution, Due to Infusion Reactions. June 28, 2018. <https://www.fda.gov/Safety/Recalls/ucm613488.htm>. Accessed January 3, 2018.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE DAPTOMYCIN PEDIATRIC CASE SERIES (N=6)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age	Sex	Country Derived	Serious Outcomes*
1	Feb 14, 2012	8404776	2	GR-CUBIST-2012S1000128	Expedited (15-Day)	56 days	F	Greece	OT
	<i>Nov 9, 2012</i>	<i>Dup 9275657</i>	<i>1</i>	<i>2012S1000128</i>	<i>Non-Expedited</i>	<i>56 days</i>	<i>F</i>	<i>Greece</i>	<i>OT</i>
2	Aug 17, 2012	8730416	1	US-CUBIST-2012S1000663	Expedited (15-Day)	7 years	M	USA	OT
	<i>Nov 9, 2012</i>	<i>Dup 9276578</i>	<i>1</i>	<i>2012S1000663</i>	<i>Expedited (15-Day)</i>	<i>7 years</i>	<i>M</i>	<i>USA</i>	<i>OT</i>
3	Sep 29, 2015	11566095	2	RU-009507513-1505RUS011022	Expedited (15-Day)	11 years	F	Russia	HO, OT
4	Dec 13, 2016	13021118	3	IT-009507513-1612ITA004978	Expedited (15-Day)	4 months	M	Italy	OT
5	Jan 17, 2018	14403410	9	US-PFIZER INC-2018018834	Expedited (15-Day)	7 years	M	USA	HO, OT
6	Mar 27, 2018	14683358	2	US-PFIZER INC-2018121195	Expedited (15-Day)	17 years	F	USA	HO
	<i>Mar 27, 2018</i>	<i>Dup 14689724</i>	<i>1</i>	<i>None</i>	<i>Direct Report</i>	<i>17 years</i>	<i>F</i>	<i>USA</i>	<i>HO</i>

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.

Abbreviations: Dup=Duplicate, F=Female, HO=Hospitalization, M=Male, OT=Other medically significant

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIMOTHY J JANCEL
02/25/2019 08:26:21 AM

IVONE E KIM
02/25/2019 08:38:06 AM

KELLY Y CAO
02/25/2019 08:45:23 AM

IDA-LINA DIAK
02/25/2019 08:51:33 AM