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

Pediatric Postmarketing Pharmacovigilance Review

Date: November 8, 2023

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Product Name: Ampicillin Injection

Pediatric Labeling Approval Date: February 15, 2018

Application Numbers/Applicants:

Application Number	Applicant
ANDA 062719	Istituto Biochimico Italiano SpA
ANDA 062772	Istituto Biochimico Italiano SpA
ANDA 062797	Istituto Biochimico Italiano SpA
ANDA 065493	Eugia Pharma Specialties Ltd
ANDA 201404	Istituto Biochimico Italiano SpA
ANDA 202198	Steriscience Pte Ltd
ANDA 090581	Sagent Pharmaceuticals Inc
ANDA 090583	Sagent Pharmaceuticals Inc
ANDA 090889	ACS Dobfar SpA
ANDA 061395	Sandoz Inc
ANDA 062738	Sandoz Inc
ANDA 063142	HQ Specialty Pharma Corp
ANDA 090354	Antibiotice Sa
ANDA 065499	Eugia Pharma Specialties Ltd
ANDA 201025	Steriscience Pte Ltd

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for ampicillin injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ampicillin injection in pediatric patients.

The National Institutes of Health (NIH), in consultation with FDA, placed ampicillin injection on a priority list of products that needed pediatric studies pursuant to section 409i of the Public Health Service (PHS) Act, which was created by BPCA. Pediatric studies for ampicillin injection were completed and based on these data, FDA determined pediatric labeling changes were appropriate. This pediatric postmarketing safety review was prompted by the pediatric labeling on February 15, 2018, that was stimulated by 409i PHS studies. The pediatric labeling included revisions to the pediatric dosing information to include neonatal dosing for meningitis and septicemia based on neonatal gestational age at birth and postnatal day of life. The labeling also added seizures to the ADVERSE REACTIONS section of the ampicillin injection product labeling.

A pediatric safety review for ampicillin injection has not previously been presented to the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with ampicillin injection in pediatric patients less than 18 years of age through August 31, 2023. DPV identified 558 reports, but all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with ampicillin injection in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for ampicillin injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ampicillin injection in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Ampicillin injection is a synthetic penicillin with broad spectrum of bactericidal activity against penicillin-susceptible Gram-positive organisms and many Gram-negative pathogens. Ampicillin was first approved by FDA in 1963 as an oral capsule formulation and the first ampicillin injection formulation was approved in 1965. **Appendix A** lists all ampicillin injection applications previously approved by FDA with their approval dates and marketing status.

The National Institutes of Health (NIH), in consultation with FDA, placed ampicillin injection on a priority list of products that needed pediatric studies in accordance to section 409I of the Public Health Service (PHS) Act, which was created by BPCA.[1] Pediatric studies for ampicillin injection were completed and based on these data, FDA determined pediatric labeling changes were appropriate.[2] This pediatric postmarketing safety review was prompted by the pediatric labeling on February 15, 2018, that was stimulated by 409I PHS studies.[1,2] The pediatric labeling included revisions to the pediatric dosing information to include neonatal dosing for meningitis and septicemia based on neonatal gestational age at birth and postnatal day of life. The labeling also added seizures to the ADVERSE REACTIONS section of the ampicillin injection product labeling.

A pediatric safety review for ampicillin injection has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The following safety information is excerpted from the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the labeling for a representative ampicillin injection application (ANDA 201025). For additional ampicillin injection labeling information, please refer to the full prescribing information.[3]

> **CONTRAINDICATIONS**
> A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.
>
> **WARNINGS**
> Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been rereported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These
> reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.
>
> There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with a penicillin, careful inquiry

should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Ampicillin for Injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General
The possibility of superinfections with mycotic organisms or bacterial pathogens should be kept in mind during therapy. In such cases, discontinue the drug and substitute appropriate treatment.

A high percentage (43 to 100 percent) of patients with infectious mononucleosis who receive ampicillin develop a skin rash. Typically, the rash appears 7 to 10 days after the start of oral ampicillin therapy and remains for a few days to a week after the drug is discontinued. In most cases, the rash is maculopapular, pruritic, and generalized. Therefore, the administration of ampicillin is not recommended in patients with mononucleosis. It is not known whether these patients are truly allergic to ampicillin.

Prescribing ampicillin for injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Laboratory Tests
As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during prolonged therapy.

Transient elevation of serum transaminase has been observed following administration of ampicillin. The significance of this finding is not known.

Drug Interactions
The concurrent administration of allopurinol and ampicillin increases substantially the incidence of skin rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients.

Drug/Laboratory Test Interactions
With high urine concentrations of ampicillin, false-positive glucose reactions may occur if Clinitest, Benedict's Solution, or Fehling's Solution are used. Therefore, it is

recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
No long-term animal studies have been conducted with this drug.

Pediatric Use
Guidelines for the administration of these drugs to children, including neonates are presented in DOSAGE AND ADMINISTRATION section.

ADVERSE REACTIONS
As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal
Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, enterocolitis, pseudomembranous colitis, and diarrhea. (These reactions are usually associated with oral dosage forms.)

Hypersensitivity Reactions
Skin rashes and urticaria have been reported frequently. A few cases of exfoliative dermatitis and erythema multiforme have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

Liver – A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown. Mild transitory SGOT elevations have been observed in individuals receiving larger (two to four times) than usual and oft-repeated intramuscular injections. Evidence indicates that glutamic oxaloacetic transaminase (GOT) is released at the site of intramuscular injection of ampicillin sodium and that the presence of increased amounts of this enzyme in the blood does not necessarily indicate liver involvement.

Hemic and Lymphatic Systems – Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System – Seizures

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 2. FAERS Search Strategy*	
Date of search	September 1, 2023
Time period of search	All dates through August 31, 2023
Search type	RxLogix Post-Market Cases
Product terms	Product Active Ingredient: Ampicillin, ampicillin sodium
MedDRA search terms (Version 26.0)	All Preferred Terms
* See **Appendix B** for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

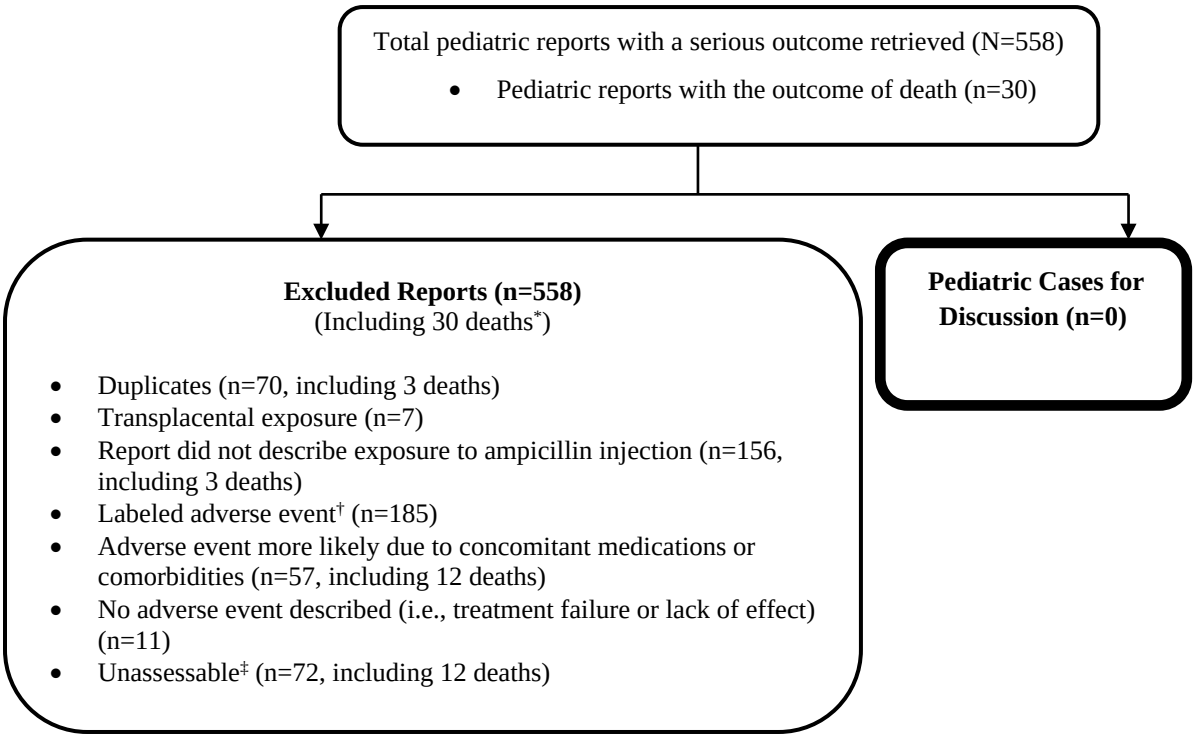
Table 2 presents the number of adult and pediatric FAERS reports through August 31, 2023, with ampicillin injection.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through August 31, 2023, With Ampicillin Injection			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	3764 (2714)	3073 (2038)	311 (151)
Pediatrics (0 - < 18 years)	994 (662)	880 (558)	84 (30)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.			

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

Our FAERS search retrieved 558 U.S. serious pediatric reports through August 31, 2023. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 558 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Ampicillin Injection



* Thirty excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to ampicillin injection. Three fatal reports were excluded due to duplicate reporting, and three fatal reports were excluded as they did not describe exposure to ampicillin injection. Of the remaining excluded reports, 12 cases described neonates who received ampicillin injection for treatment of suspected infections during complicated clinical courses in the neonatal intensive care unit. All 12 neonates died due to septic complications. An additional 12 cases reported fatal outcomes, but the cases lacked sufficient clinical information to assess the adverse event or the events' relationship with ampicillin injection.

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

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

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

There are no fatal pediatric adverse event cases for discussion.

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

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

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with ampicillin injection in pediatric patients less than 18 years of age through August 31, 2023. DPV identified 558 reports, but all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with ampicillin injection in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

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7 APPENDICES

7.1 APPENDIX A. AMPICILLIN INJECTION APPLICATIONS

Trade Name	Product Active Ingredient	Application Number	Dosage Form	Initial Approval Date	Sponsor	Marketing Status
--	Ampicillin sodium	ANDA 061395	Injectable, injection	3/3/1971	Sandoz Inc	Marketed
--	Ampicillin sodium	ANDA 061936	Injectable, injection	11/24/1976	Consolidated Pharmaceutical Group Inc	Discontinued[4]
--	Ampicillin sodium	ANDA 062692	Injectable, injection	6/24/1986	Hikma Pharmaceuticals USA Inc	Discontinued[5]
--	Ampicillin sodium	ANDA 062634	Injectable, injection	1/9/1987	International Medication Systems Ltd	Discontinued[6]
--	Ampicillin sodium	ANDA 062738	Powder, intravenous	2/19/1987	Sandoz Inc	Marketed
--	Ampicillin sodium	ANDA 062719	Injectable, injection	5/12/1987	Istituto biochimico Italiano SpA	Marketed
--	Ampicillin sodium	ANDA 062860	Injectable, injection	2/5/1988	Apothecon Inc	Discontinued[7]
--	Ampicillin sodium	ANDA 062994	Injectable, injection	9/15/1988	Watson Laboratories Inc	Discontinued[8]
--	Ampicillin sodium	ANDA 062816	Injectable, injection	10/28/1988	Watson Laboratories Inc	Discontinued[8]
--	Ampicillin sodium	ANDA 062565	Injectable, injection	11/22/1988	Eli Lily and Co	Discontinued[9]
--	Ampicillin sodium	ANDA 063142	Injectable, injection	4/15/1993	HQ Specialty Pharma Corp	Marketed
--	Ampicillin sodium	ANDA 063147	Injectable, injection	4/15/1993	GC Hanford Manufacturing Co	Discontinued[10]
--	Ampicillin sodium	ANDA 062772	Injectable, injection	4/15/1993	Istituto biochimico Italiano SpA	Marketed
--	Ampicillin sodium	ANDA 062797	Injectable, injection	7/12/1993	Istituto biochimico Italiano SpA	Marketed
--	Ampicillin sodium	ANDA 090354	Injectable, injection	12/28/2009	Antibiotice SA	Marketed

Trade Name	Product Active Ingredient	Application Number	Dosage Form	Initial Approval Date	Sponsor	Marketing Status
--	Ampicillin sodium	ANDA 065499	Injectable, injection	8/17/2010	Eugia Pharma Specialties Ltd	Marketed
--	Ampicillin sodium	ANDA 065493	Injectable, injection	8/17/2010	Eugia Pharma Specialties Ltd	Marketed
--	Ampicillin sodium	ANDA 090884	Injectable, injection	4/3/2013	ACS Dobfar SpA	Discontinued[11]
--	Ampicillin sodium	ANDA 090889	Injectable, injection	4/3/2013	ACS Dobfar SpA	Marketed
--	Ampicillin sodium	ANDA 201404	Injectable, injection	12/20/2013	Istituto biochimico Italiano SpA	Marketed
--	Ampicillin sodium	ANDA 202198	Injectable, injection	4/7/2014	Steriscience Private Ltd	Marketed
--	Ampicillin sodium	ANDA 201025	Injectable, injection	4/9/2014	Steriscience Private Ltd	Marketed
--	Ampicillin sodium	ANDA 202864	Injectable, injection	9/4/2015	Hospira Inc	Discontinued[12]
--	Ampicillin sodium	ANDA 202865	Injectable, injection	9/4/2015	Hospira Inc	Discontinued[12]
--	Ampicillin sodium	ANDA 090581	Injectable, injection	10/20/2015	Sagent Pharmaceuticals Inc	Marketed
--	Ampicillin sodium	ANDA 090583	Injectable, injection	11/27/2015	Sagent Pharmaceuticals Inc	Marketed
Omnipen-N	Ampicillin sodium	ANDA 060626	Injectable, injection	4/28/1967	Wyeth Ayerst	Discontinued[13]
Omnipen-N	Ampicillin sodium	ANDA 062718	Injectable, injection	12/16/1986	Wyeth Ayerst	Discontinued[13]
Penbritin-S	Ampicillin sodium	NDA 050072	Injectable, injection	12/29/1966	Wyeth Ayerst	Discontinued[14]
Polycillin-N	Ampicillin sodium	NDA 050309	Injectable, injection	3/29/1965	Bristol Laboratories Inc	Discontinued[14]
Totacillin-N	Ampicillin sodium	ANDA 060677	Injectable, injection	5/4/1976	GlaxosmithKline	Discontinued[15]
Totacillin-N	Ampicillin sodium	ANDA 062727	Injectable, injection	12/19/1986	GlaxosmithKline	Discontinued[15]

Abbreviations: ANDA=abbreviated new drug application, Co=company, Corp=corporation, Inc=incorporated, Ltd=limited company, NDA=new drug application

7.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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

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

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