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: May 22, 2024

Reviewers: Ivone Kim, MD
Division of Pharmacovigilance I

Team Leader: Carmen Cheng, PharmD
Division of Pharmacovigilance I

Division Director: Monica Muñoz, PharmD, PhD, BCPS
Division of Pharmacovigilance I

Pediatric Labeling Approval Dates:
March 4, 2020
March 9, 2020
December 4, 2021
September 1, 2022

New Drug Application (NDA)	Product Name	Product Active Ingredient	Formulation	Applicant
050162	Cleocin hydrochloride	Clindamycin hydrochloride	Capsule	Pfizer
050441	Cleocin phosphate	Clindamycin phosphate	Injectable	Pfizer
050639	Cleocin phosphate in dextrose 5% in plastic container	Clindamycin phosphate	Injectable	Pfizer
208083	Clindamycin phosphate in 0.9% sodium chloride	Clindamycin phosphate	Intravenous solution	Baxter Healthcare Corporation

TTT Record ID: 2023-7545

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for clindamycin in pediatric patients less than 17 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 clindamycin intravenous (IV) and oral (PO) formulations in pediatric patients.

Section 409I of BPCA requires that FDA and the National Institutes of Health (NIH) develop and publish a priority list of therapeutic areas in critical need of pediatric research. FDA receives these data for consideration of labeling changes. In accordance with BPCA, the National Institute of Child Health and Human Development (NICHD) prioritized clindamycin (IND 140739, 115396) for evaluation and sponsored two pediatric studies: study NICHD-2012-CLIN01 (NCT01744730) entitled "Safety and pharmacokinetics of multiple-dose intravenous and oral clindamycin in pediatric subjects with BMI $\geq 85^{th}$ percentile" and study NICHD-203-ABS01 (NCT01994993) entitled "Antibiotic safety in infants with complicated intra-abdominal infections (SCAMP)."

FDA updated the labeling for clindamycin based on data from NICHD-2012-CLIN01 and NICHD-203-ABS01. On March 4, 2020 (NDA 050639) and March 9, 2020 (NDA 050162, 050441), the clindamycin labeling was updated to indicate that that clindamycin clearance and volume of distribution, normalized by total body weight, are comparable regardless of obesity in children aged 2 to <18 years. On December 4, 2021 (NDA 050441, 050639) and September 1, 2022 (NDA 208083), the clindamycin injection labeling was updated to include dosing guidance for use in pediatric patients based on pharmacokinetic safety data.

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes listed above. DPV has not previously performed a postmarketing safety evaluation for clindamycin for the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with clindamycin IV and PO formulations in pediatric patients less than 17 years of age from February 22, 1970 – January 31, 2024, and identified 277 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with clindamycin IV or PO formulations in pediatric patients less than 17 years of age.

DPV did not identify any new pediatric safety concerns for clindamycin IV or PO formulations at this time and will continue routine pharmacovigilance monitoring for clindamycin.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for clindamycin in pediatric patients less than 17 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 clindamycin intravenous (IV) and oral (PO) formulations in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin. Clindamycin is available in multiple formulations including capsules, injectables, solutions, lotions, gels, creams, and swabs. This review focuses on clindamycin IV injection, IV solution, and PO capsule formulations. FDA first approved clindamycin in 1970. Clindamycin IV and PO formulations are currently indicated for the following:[1,2]

- Serious infections caused by susceptible anaerobic bacteria
- Infections due to susceptible isolates of streptococci, pneumococci, and staphylococci
- Lower respiratory tract infections
- Skin and skin structure infections
- Gynecological infections
- Intra-abdominal infections
- Septicemia
- Bone and joint infections

Section 409I of BPCA requires that FDA and the National Institutes of Health (NIH) develop and publish a priority list of therapeutic areas in critical need of pediatric research. FDA receives these data for consideration of labeling changes. In accordance with BPCA, the National Institute of Child Health and Human Development (NICHD) prioritized clindamycin (IND 140739, 115396) and sponsored two pediatric studies:

> Study NICHD-2012-CLIN01 (NCT01744730) entitled "Safety and pharmacokinetics of multiple-dose intravenous and oral clindamycin in pediatric subjects with BMI $\geq 85^{th}$ percentile" was a prospective, open-label safety and pharmacokinetic (PK) study of multiple doses of PO and IV clindamycin in overweight and obese children aged 2 - <18 years. Duration of therapy was up to 14 days. A total of 23 participants were enrolled, 22 were analyzed for safety and 21 were analyzed for PK. Additional clindamycin PK data in pediatric patients were used from other NICHD studies to develop the population PK model.[3]
>
> Study NICHD-203-ABS01 (NCT01994993) entitled "Antibiotic safety in infants with complicated intra-abdominal infections (SCAMP)" was a prospective, open-label, partially randomized multicentral safety study that examined the PK and efficacy of tiered IV multi-drug dosing schemes based on postmenstrual age. Dosing was determined using population PK modeling and simulations. Patients were treated with a clindamycin containing regimen for up to 10 days.[4]

FDA reviewed data from completed studies NICHD-2012-CLIN01 and NICHD-203-ABS01. Based on these data, FDA approved the following pediatric labeling changes:

> Based on study NICHD-2012-CLIN01, the labeling for clindamycin PO and IV formulations was updated on March 4, 2020 (NDA 050639), and March 9, 2020 (NDA 050162, 050441), to indicate that that clindamycin clearance and volume of distribution, normalized by total body weight, are comparable regardless of obesity in children aged 2 to <18 years.[3]
>
> Based on findings from study NICHD-203-ABS01, FDA updated the labeling for clindamycin injection to include dosing guidance for use in pediatric patients based on PK safety data. The labeling was updated on December 4, 2021 (NDA 050441, 050639) and September 1, 2022 (NDA 208083).[4]

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on March 4, 2020, March 9, 2020, December 4, 2021, and September 1, 2022. DPV has not previously performed a postmarketing safety evaluation for clindamycin for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The clindamycin phosphate in sodium chloride injection (NDA 208083) labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection.[2] For additional clindamycin IV injection, IV solution, and PO capsule labeling information, please refer to the full prescribing information.[1,2]

WARNING: *CLOSTRIDIOIDES DIFFICILE*-ASSOCIATED DIARRHEA (CDAD) and COLITIS
See full prescribing information for complete boxed warning.

***Clostridioides difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Clindamycin Phosphate in Sodium Chloride 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* (5.1).**

Because Clindamycin Phosphate in Sodium Chloride Injection therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate (1). It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy (5.1).

----------CONTRAINDICATIONS ----------
Individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

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

- Anaphylactic shock, anaphylactic reactions and severe hypersensitivity reactions have been reported. Discontinue treatment if such reactions occur.
- Cases with acute kidney injury (AKI) have been reported during treatment with clindamycin. Consider renal function monitoring, particularly in certain patients (e.g., those with pre-

existing renal dysfunction). Discontinue treatment if AKI occurs and no other etiology is identified.

- Elderly patients with associated severe illness may have a greater risk of developing adverse reactions from diarrhea. Monitor these patients carefully for change in bowel frequency.
- Avoid use of Clindamycin Phosphate in Sodium Chloride Injection in individuals with a history of gastrointestinal disease, particularly colitis.
- Avoid use of Clindamycin Phosphate in Sodium Chloride Injection in atopic individuals.
- During prolonged therapy, perform periodic liver and kidney function tests and blood counts.
- The use of Clindamycin Phosphate in Sodium Chloride Injection may result in overgrowth of nonsusceptible organisms-particularly yeasts. Take appropriate measures, if this occurs.

----------ADVERSE REACTIONS----------
Most common adverse reactions: gastrointestinal (abdominal pain, nausea, vomiting) and hypersensitivity reactions (anaphylaxis, urticaria, skin rash).

8.4 Pediatric Use

Clindamycin Phosphate in Sodium Chloride Injection is indicated for the treatment of serious infections caused by susceptible anaerobic bacteria, infections due to susceptible isolates of streptococci, pneumococci and staphylococci, lower respiratory tract Infections, skin and skin structure infections, gynecological infections, intra-abdominal infections, septicemia and bone and joint infections in pediatric patients for whom appropriate dosing with this formulation can be achieved [see Indications and Usage (1.1-1.8)] and Dosage and Administration (2.3)].

When Clindamycin Phosphate in Sodium Chloride Injection is administered to the pediatric population (less than 1 month to 16 years old) appropriate dosing and monitoring of organ system functions is desirable. Because of the limitations of the available strengths and administration requirements (i.e., administration of fractional doses is not recommended) of Clindamycin Phosphate in Sodium Chloride Injection, and to avoid unintentional overdose, this product is not recommended for use if a dose of Clindamycin Phosphate in Sodium Chloride Injection is required that does not equal 300 mg 600 mg or 900 mg is required and an alternative formulation of clindamycin should be considered [see Dosage and Administration (2.3)].

The potential for the toxic effect in the pediatric population from chemicals that may leach from the single dose premixed Clindamycin Phosphate in Sodium Chloride Injection preparation in plastic has not been evaluated.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 1. FAERS Search Strategy*	
Date of search	February 12, 2024
Time period of search	February 22, 1970† – January 31, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Clindamycin, clindamycin hydrochloride, clindamycin hydrochloride monohydrate, clindamycin phosphate
Other Search Terms	Dose route of administration: Intravenous (not otherwise specified), intramuscular, intravenous bolus, intravenous drip, parenteral, oral
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database † Initial U.S. approval date for clindamycin PO formulation Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from February 22, 1970 – January 31, 2024, with clindamycin IV and PO formulations.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 22, 1970, through January 31, 2024, with Clindamycin IV and PO Formulations

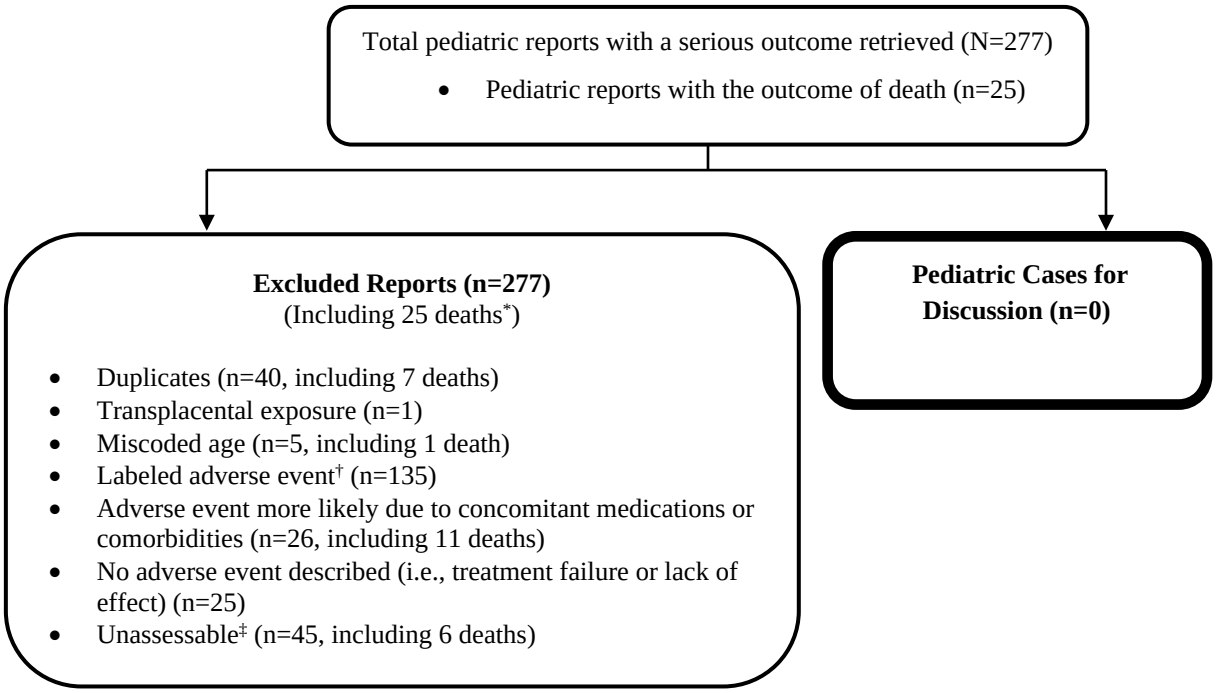
	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	9,086 (4,003)	7,946 (3,016)	776 (316)
Pediatrics (0 - < 17 years)	652 (364)	556 (277)	36 (25)

* 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 277 U.S. serious pediatric reports from February 22, 1970 – January 31, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded 277 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 Clindamycin IV and PO Formulations



* Twenty-five excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to clindamycin IV or PO formulations. One death report involved an adult patient who died from pulmonary failure. Eleven cases described pediatric patients who died from complications from their primary medical conditions (e.g., heart transplant, oncological diseases, complications from

malaria, prematurity, necrotizing enterocolitis). Six death cases lacked sufficient clinical information to perform a causality assessment with clindamycin.

† 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 clindamycin IV and PO formulations in pediatric patients less than 17 years of age from February 22, 1970 – January 31, 2024, and identified 277 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with clindamycin IV or PO formulations in pediatric patients less than 17 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for clindamycin IV or PO formulations at this time and will continue routine pharmacovigilance monitoring for clindamycin.

6 REFERENCES

1. Cleocin HCl (clindamycin hydrochloride) capsules [Prescribing information]. New York, NY. Pfizer. May 2022.
2. Clindamycin phosphate in sodium chloride injection [Prescribing information]. Deerfield, IL; Baxter Healthcare Corporation. September 2022.
3. Memorandum. Clindamycin IND 115396. October 10, 2019. Available at: https://www.regulations.gov/document/FDA-2019-N-4338-0001
4. Memorandum. Clindamycin IND 140739. February 22, 2021. Available at: https://www.regulations.gov/document/FDA-2021-N-0142-0001

7 APPENDICES

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

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

Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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

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