Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

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TTT Record ID: 2025-15333

Product Trade Name	**Generic Name**	**Application Number**	**Applicant**	**Pediatric Labeling date**
Kloxxado nasal spray	Naloxone	NDA 212045	Hikma Pharmaceuticals USA, Inc.	04/29/2021
Zimhi injection	Naloxone hydrochloride	NDA 212854	Adamis Pharmaceuticals Corporation	10/15/2021
Naloxone Hydrochloride Autoinjector	Naloxone hydrochloride	NDA 215457	Kaleo, Inc	02/28/2022
Rextovy nasal spray	Naloxone hydrochloride	NDA 208969	Amphastar Pharmaceuticals, Inc.	03/07/2023
RiVive nasal spray	Naloxone hydrochloride	NDA 217722	Harm Reduction Therapeutics, Inc.	07/28/2023
Rezenopy nasal spray	Naloxone hydrochloride	NDA 215487	Summit Biosciences Inc.	04/19/2024

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for naloxone products in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with naloxone in pediatric patients. Naloxone is an opioid antagonist used for the emergency treatment of known or suspected opioid overdose. FDA approved the first naloxone product on April 13, 1971. FDA approved naloxone under several new drug applications (NDAs). Naloxone is available by prescription and as over-the-counter formulations.

This pediatric postmarketing safety review was prompted by the following pediatric labeling for the initial approval of the following naloxone products:

- April 29, 2021: Kloxxado (NDA 212045)
- October 15, 2021: Zimhi (NDA 212854)
- February 28, 2022: Naloxone hydrochloride autoinjector (NDA 215457)
- March 7, 2023: Naloxone hydrochloride nasal spray (NDA 208969)
- July 28, 2023: RiVive nasal spray (NDA 217722)
- April 19, 2024: Rezenopy nasal spray (NDA 215487)

On February 12, 2019, DPV completed a review of postmarketing adverse event reports with a serious outcome for Narcan (naloxone hydrochloride) nasal spray (NDA 208411) in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Narcan. On March 28, 2019, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

DPV reviewed all U.S. serious FAERS reports with naloxone in pediatric patients less than 18 years of age through May 20, 2025, and identified 111 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 naloxone in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for naloxone products in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with naloxone in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Naloxone is an opioid antagonist used for the emergency treatment of known or suspected opioid overdose. FDA approved the first naloxone product on April 13, 1971.[1] FDA approved naloxone under several new drug applications (NDAs). Naloxone is available by prescription and as over-the-counter formulations. **Appendix A** lists the single-ingredient naloxone products approved by FDA.

This pediatric postmarketing safety review was prompted by the following pediatric labeling for naloxone products:

- April 29, 2021: Labeling for the initial approval for Kloxxado nasal spray (NDA 212045) for the emergent treatment of known or suspected opioid overdose in adult and pediatric patients.
- October 15, 2021: Labeling for the initial approval of Zimhi injection (NDA 212854) for the emergency treatment of known or suspected opioid overdose in adult and pediatric patients.
- February 28, 2022: Labeling for the initial approval of Naloxone hydrochloride autoinjector (NDA 215457) for the use by military personnel and chemical incident responders for 1) emergency treatment of patients ≥12 years where use of high-potency opioids such as fentanyl analogues as chemical weapon is suspected and 2) temporary prophylaxis of respiratory and/or central nervous system depression in military personnel and chemical incident responders entering an area contaminated with high-potency opioids such as fentanyl analogues.
- March 7, 2023: Labeling for the initial approval for Naloxone hydrochloride nasal spray (NDA 208969)[a] for the emergency treatment of known or suspected opioid overdose in adult and pediatric patients.
- July 28, 2023: Labeling for the initial approval of RiVive nasal spray (NDA 217722) for over-the-counter use for emergency treatment of opioid overdose in adult and pediatric patients.
- April 19, 2024: Labeling for the initial approval of Rezenopy nasal spray (NDA 215487) for emergency treatment of known or suspected opioid overdose in adult and pediatric patients.

On February 12, 2019, DPV completed a review of postmarketing adverse event reports with a serious outcome for Narcan (naloxone hydrochloride) nasal spray (NDA 208411) in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Narcan. On March 28, 2019, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.[3]

[a] NDA 208969 is now marketed under the proprietary name Rextovy.[2]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Zimhi and Kloxxado labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional naloxone labeling information, please refer to the full prescribing information (see **Appendix A**).

Zimhi (naloxone hydrochloride injection) labeling[10]

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

Hypersensitivity to naloxone hydrochloride or to any of the other ingredients in ZIMHI. (4)

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

- Risk of Recurrent Respiratory and CNS Depression: Due to the duration of action of naloxone relative to the opioid, respiratory and CNS depression may recur after the first dose of naloxone. Seek emergency medical assistance immediately after the first dose, keep the patient under continued surveillance, and administer repeated doses of naloxone using a new ZIMHI, as necessary, while awaiting emergency medical assistance. (5.1)
- Risk of Limited Efficacy with Partial Agonists or Mixed Agonists/Antagonists: Reversal of respiratory depression caused by partial agonists or mixed agonists/antagonists such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses may be required. (5.2)
- Precipitation of Severe Opioid Withdrawal: Use in patients who are opioid dependent results in rapid onset of opioid withdrawal. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. Monitor for the development of opioid withdrawal. (5.3)
- Risk of Cardiovascular (CV) Effects: Abrupt postoperative reversal of opioid depression may result in adverse CV effects. These events have primarily occurred in patients who had pre-existing CV disorders or received other drugs that may have similar CV effects. Monitor these patients closely in an appropriate healthcare setting after use of naloxone hydrochloride. (5.3)
- Risk of Accidental Needlestick Injury: After use, the ZIMHI needle is exposed until the safety guard is deployed. Stress to patients the importance of familiarizing themselves with the device and its operation prior to experiencing an emergency situation, and to immediately seek medical attention should a needlestick occur. (5.4)

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

The following adverse reactions were most commonly observed in ZIMHI clinical studies: nausea, dizziness, lightheadedness, and elevated bilirubin. (6)

8.4 Pediatric Use

The safety and effectiveness of ZIMHI™ (for intramuscular and subcutaneous use) have been established in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression. Use of naloxone hydrochloride in all pediatric patients is supported by adult bioequivalence studies coupled with evidence from the safe and effective use of another naloxone hydrochloride injectable product. No pediatric studies were conducted for ZIMHI.

Absorption of naloxone hydrochloride following subcutaneous or intramuscular administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds appropriately to naloxone hydrochloride injection, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

In opioid-dependent pediatric patients, (including neonates), administration of naloxone hydrochloride may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid

withdrawal symptoms. Unlike acute opioid withdrawal in adults, acute opioid withdrawal in neonates manifesting as seizures may be life-threatening if not recognized and properly treated. Other signs and symptoms in neonates may include excessive crying and hyperactive reflexes. In these settings where it may be preferable to avoid the abrupt precipitation of acute opioid withdrawal symptoms, consider use of an alternative, naloxone hydrochloride product that can be dosed according to weight and titrated to effect. [see Warnings and Precautions (5.3)].

In pediatric patients under the age of one year, the caregiver should pinch the thigh muscle while administering ZIMHI. Carefully observe the administration site for evidence of residual needle parts, signs of infection, or both. [see Dosing Information (2.2)].

Kloxxado (naloxone hydrochloride) nasal spray labeling:[9]

----------CONTRAINDICATIONS ----------
Hypersensitivity to naloxone hydrochloride or to any of the other ingredients. (4)

----------WARNINGS AND PRECAUTIONS ----------
- Risk of Recurrent Respiratory and CNS Depression: Due to the duration of action of naloxone relative to the opioid, keep patient under continued surveillance and administer repeat doses of naloxone using a new nasal spray with each dose, as necessary, while awaiting emergency medical assistance. (5.1)
- Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists: Reversal of respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses may be necessary. (5.2)
- Precipitation of Severe Opioid Withdrawal: Use in patients who are opioid dependent may precipitate opioid withdrawal. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. Monitor for the development of opioid withdrawal. (5.3)
- Risk of Cardiovascular (CV) Effects: Abrupt postoperative reversal of opioid depression may result in adverse CV effects. These events have primarily occurred in patients who had preexisting CV disorders or received other drugs that may have similar adverse CV effects. Monitor these patients closely in an appropriate healthcare setting after use of naloxone hydrochloride. (5.3)

----------ADVERSE REACTIONS ----------
The following adverse reactions were reported with KLOXXADO in two adult subjects each: abdominal pain, asthenia, dizziness, headache, nasal discomfort, and presyncope. (6.1)

8.4 Pediatric Use

The safety and effectiveness of KLOXXADO has been established in pediatric patients of all ages for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression. Use of naloxone hydrochloride in pediatric patients is supported by evidence from adult bioavailability studies with additional evidence from the reported safe and effective use of other naloxone hydrochloride products. No pediatric studies were conducted for KLOXXADO.

Absorption of naloxone hydrochloride following intranasal administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds appropriately to naloxone hydrochloride, he/she must be carefully monitored for at least 24 hours, as a relapse may occur as naloxone hydrochloride is metabolized.

In opioid-dependent pediatric patients, (including neonates), administration of naloxone hydrochloride may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. Unlike acute opioid withdrawal in adults, acute opioid withdrawal in neonates manifesting as seizures may be life-threatening if not recognized and properly treated. Other signs and symptoms in neonates may include excessive crying and hyperactive reflexes. In these settings where it

may be preferable to avoid the abrupt precipitation of acute opioid withdrawal symptoms, consider use of an alternative, naloxone hydrochloride product that can be dosed according to weight and titrated to effect [see Warnings and Precautions (5.3)].

Also, in situations where the primary concern is for infants at risk for opioid overdose, consider whether the availability of alternate naloxone-containing products may be better suited than KLOXXADO.

Juvenile Animal Study

In a juvenile animal study, male and female juvenile rats were administered a single intranasal dose of saline, vehicle consisting of 20% alcohol and 5% propylene glycol, or naloxone (123 mg/kg, 185 mg/kg, and 246 mg/kg) on postnatal day 7 (PND 7). There were no test article-related findings on sexual maturation, neuroapoptosis, or on a limited number of neurocognitive endpoints which included social interactions as well as learning and memory. The no-effect dose level for neurodevelopmental toxicity was the high dose tested, which is 6.8-times a neonate dose from two nasal sprays of KLOXXADO based on body surface area comparison and a neonate weight of 2.5 kg.

2 METHODS AND MATERIALS

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

Table 1. FAERS Search Strategy[*]

Date of search	May 21, 2025
Time period of search	All dates through May 20, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: Naloxone, naloxone hydrochloride
MedDRA search terms (Version 28.0)	All Preferred Terms

[*] See **Appendix B** for a description of the FAERS database
Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities

3 RESULTS

3.1 SELECTION OF U.S. SERIOUS PEDIATRIC CASES IN FAERS

Our FAERS search retrieved 111 U.S. serious[b] pediatric reports for patients less than 18 years old through May 20, 2025,[c] including 52 reports with the outcome of death. We excluded all 111 reports from the case series for the reasons described below:

- Duplicates (n=46, including 24 deaths)
- Transplacental exposure (n=3, including 1 death)
- Labeled adverse event not representing increased severity (n=6)
- The patient had no exposure to naloxone (n=1)

[b] 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.
[c] Includes two pediatric reports identified among reports not coded with an age.

- Adverse event more likely due to concomitant medications or comorbidities (n=44, including 24 deaths)
- No adverse event described (i.e., treatment failure or lack of effect) (n=1)
- Unassessable[d] (n=10, including 3 deaths)

Of excluded U.S. FAERS reports, 52 reports described fatal outcomes. After accounting for duplicate reports (n=24), we identified 28 unique cases describing fatal outcomes. None of the deaths were determined to be attributed to naloxone. One case described fetal death after maternal multi-substance overdose. Twenty-four cases described death due to toxicities following single-substance (n=14; opioid (n=11), anesthetic (n=1), non-steroidal anti-inflammatory drug (n=1), metformin (n=1)) or multi-substance (n=10, including opioids, benzodiazepines, antihistamines, selective serotonin reuptake inhibitors, anticonvulsants, illicit substances, amphetamines, or veterinary products) ingestions. One case described death due to genetic cardiac condition. Two cases did not provide sufficient clinical details to understand cause of death or determine causality relative to naloxone exposure.

3.2 SUMMARY OF U.S. FATAL PEDIATRIC CASES (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.3 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 naloxone in pediatric patients less than 18 years of age through May 20, 2025, and identified 111 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 naloxone in pediatric patients less than 18 years of age.

5 CONCLUSION

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

[d] Unassessable reports are those that 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.

6 REFERENCES

1. Narcan (naloxone hydrochloride) NDA 016636. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016636 Accessed June 25,
2. Rextovy (naloxone hydrochloride) nasal spray. [Prescribing information]. El Monte, CA; International Medication Systems, Limited: June 2023
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4. Narcan (naloxone hydrochloride injection, USP). [Prescribing information]. Chadds Ford, PA; Endo Pharmaceuticals, Inc.: April 2004.
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6. Narcan (naloxone HCl nasal spray 4mg). Drug facts label. Plymouth Meeting, PA; Emergent Devices, Inc.; March 2023: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208411Orig1s006lbl.pdf
7. Narcan (naloxone hydrochloride) nasal spray. [Prescribing information]. Plymouth meeting, PA; Emergent Devices, Inc.: May 2023.
8. Evzio (naloxone hydrochloride injection) Auto-Injector for intramuscular or subcutaneous use. [Prescribing information]. Richmond, VA; Kaleo, Inc.: October 2016.
9. Kloxxado (naloxone hydrochloride) nasal spray. [Prescribing information]. Columbus, OH: Hikma Specialty USA, Inc.: April 2021.
10. Zimhi (naloxone hydrochloride injection) for intramuscular or subcutaneous use. [Prescribing information]. San Diego, CA; Adamis Pharmaceuticals: October 2021.
11. Naloxone Hydrochloride injection for intramuscular or subcutaneous use. [Prescribing information]. Richmond, VA; Kaleo, Inc.: February 2022.
12. Rezenopy (naloxone hydrochloride) nasal spray. [Prescribing information]. Lexington, KY; Summit Biosciences, Inc.: April 2024.

7 APPENDICES

7.1 APPENDIX A. SINGLE-INGREDIENT NALOXONE PRODUCTS APPROVED BY FDA

Proprietary Name	NDA	Initial Approval Date	Dosage Form/Route	Strength	Marketing Status	Pediatric Indication
Narcan[4]	016636	4/13/1971	Injectable; injection	0.4 mg/ml, 0.02 mg/ml, 1 mg/ml	Discontinued	Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine. Also indicated for diagnosis of suspected or known acute opioid overdosage.
Evzio[5]	205787	4/3/2014	Solution; intramuscular, subcutaneous	0.4 mg/ 0.4 ml	Discontinued	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Narcan[6,7]	208411	11/18/2015	Spray, metered; nasal	4 mg/spray	Over-the-counter	To "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin.
				2 mg/spray	Discontinued	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Evzio[8]	209862	10/19/2016	Solution; intramuscular, subcutaneous	2 mg/0.4 ml	Discontinued	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients.
Kloxxado[9]	212045	4/29/2021	Spray; nasal	8 mg/spray	Prescription	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, for adult and pediatric patients.
Zimhi[10]	212854	10/15/2021	Solution; intramuscular, subcutaneous	5 mg/0.5 ml	Prescription	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adult and pediatric patients

Proprietary Name	NDA	Initial Approval Date	Dosage Form/Route	Strength	Marketing Status	Pediatric Indication
Naloxone Hydrochloride[11]	215457	2/28/2022	Solution; intramuscular, subcutaneous	10 mg/0.4 ml	Discontinued	For use by military personnel and chemical incident responders for: • Emergency treatment of patients ≥12 years of age where use of high-potency opioids such as fentanyl analogues as a chemical weapon is suspected • Temporary prophylaxis of respiratory and/or central nervous system depression in military personnel and chemical incident responders entering an area contaminated with high-potency opioids such as fentanyl analogues
Rextovy[2]	208969	3/7/2023	Spray, metered: nasal	4 mg/spray	Prescription	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients.
Rezenopy[12]	215487	4/19/2024	Spray; nasal	10 mg/spray	Prescription	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adult and pediatric patients.

Abbreviations: mg=milligram, ml=milliliter, 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.