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**Pediatric Postmarketing Pharmacovigilance**

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**Product Name:** Narcan (naloxone) nasal spray

**Pediatric Labeling  
Approval Date:** November 18, 2015

**Application Type/Number:** 208411

**Applicant/Sponsor:** Adapt Pharma Operations Limited

**OSE RCM #:** 2018-2545

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## **EXECUTIVE SUMMARY**

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Narcan (naloxone) nasal spray in pediatric patients through age 17 years. 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 Narcan (naloxone) nasal spray in pediatric patients.

The FDA approved Narcan (naloxone) nasal spray on November 18, 2015 and it is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients of all ages.

We reviewed all FAERS reports with Narcan (naloxone) nasal spray in the pediatric population through age <17 years during the period November 18, 2014 to November 19, 2018. There were no pediatric cases with a serious outcome identified during this time period.

DPV did not identify any new pediatric safety concerns for Narcan (naloxone) nasal spray and recommends no regulatory action at this time. We will continue to monitor all adverse events associated with the use of Narcan (naloxone) nasal spray.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Narcan (naloxone) nasal spray in pediatric patients through age 17 years. 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 Narcan (naloxone) nasal spray in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Narcan injection is an opioid antagonist first approved on April 13, 1971 for 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, and butorphanol and cyclazocine. Narcan injection is also indicated for the diagnosis of suspected or known acute opioid overdose. Narcan injection is approved for use in pediatric patients of all ages. Narcan injection may be administered intravenously, intramuscularly, or subcutaneously.<sup>1</sup>

Table 1 lists FDA approved products containing naloxone. Of note, the injectable Narcan product (NDA 016636) has been discontinued, but generic injectable naloxone products are currently marketed (see Appendix A for list).

<b>Application No.</b>	<b>Brand Name</b>	<b>Strength</b>	<b>Dosage Form/Route of Administration</b>	<b>Manufacturer</b>	<b>Approval Year</b>	<b>Population for Use</b>
NDA 016636	Narcan	0.4 mg/ml, 0.02 mg/ml, 1 mg/ml	Injectable/Injection	Adapt Pharma	1971 (discontinued)	Pediatric patients (all ages), adults
NDA 205787	Evzio	0.4 mg/0.4 ml	Solution/IM, SC	Kaleo	2014 (discontinued)	Pediatric patients (all ages), adults
NDA 209862	Evzio	2 mg/0.4 ml	Solution/IM, SC	Kaleo	2016	Pediatric patients (all ages), adults
NDA 208411	Narcan nasal spray	2 mg/0.1 ml*, 4 mg/0.1 ml spray	Spray, metered/Nasal	Adapt Pharma	2015	Pediatric patients (all ages), adults

IM: intramuscular; SC: subcutaneous  
\* Narcan nasal spray 2 mg/0.1 ml strength is discontinued.

On November 18, 2015, FDA approved Narcan (naloxone) nasal spray (NDA 208411) via a 505(b)(2) pathway relying on the published literature. A generic naloxone product (International Medication System, ANDA 072076) was utilized in a relative bioavailability study to cross-reference the efficacy and safety information from the Narcan injection product (NDA

016636).<sup>a,2</sup> Narcan (naloxone) nasal spray is approved for the indication of the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients of all ages.

Narcan (naloxone) nasal spray was initially approved as a fixed 4-mg dosing regimen in pediatric patients compared to weight-based dosing with injectable products. A literature-based pediatric assessment was submitted in the application, as efficacy and pharmacokinetic studies were determined to be infeasible in pediatric patients due to ethical and technical challenges, and the product was labeled for all pediatric populations. FDA issued the Sponsor two postmarketing requirements (PMRs). PMR 2990-1 required the Sponsor to establish reliability requirements for Narcan (naloxone) nasal spray, and complete testing that verifies the product's reliability and PMR 2990-2 required the Sponsor to monitor for the detection and evaluation of under-dosing and failure-to-dose events with Narcan (naloxone) nasal spray.<sup>3</sup>

This review was prompted by the approval of Narcan (naloxone) nasal spray. DPV has not presented Narcan (naloxone) nasal spray before the Pediatric Advisory Committee (PAC).

## 1.2 SELECT LABELED SAFETY INFORMATION

Select safety information from the Narcan (naloxone) nasal spray product label dated January 2017 is included below:<sup>4</sup>

-----CONTRAINDICATIONS-----  
Hypersensitivity to naloxone hydrochloride. (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 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 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 observed in a NARCAN Nasal Spray clinical study: increased blood pressure, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, and nasal inflammation. (6)

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<sup>a</sup> Adapt Pharma, Inc. owned both Narcan (naloxone) nasal spray (NDA 208411) and Narcan injection (NDA 16636) at the time of Narcan (naloxone) spray approval. Adapt Pharma, Inc submitted bioavailability data to cross-reference their Narcan injection (NDA 16636); however, Narcan injection (NDA 16636) products were discontinued from the market. Therefore, a generic naloxone product (ANDA 072076) was used to create a scientific bridge to their Narcan injection (NDA 16636).

The following adverse reactions have been identified primarily during post-approval use of naloxone hydrochloride in the post-operative setting. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation.

#### 8.4 Pediatric Use

The safety and effectiveness of NARCAN Nasal Spray have 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 all pediatric patients is supported by adult bioequivalence studies coupled with evidence from the safe and effective use of other naloxone hydrochloride drug products. No pediatric studies were conducted for NARCAN Nasal Spray.

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. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening, if not recognized, and should be treated according to protocols developed by neonatology experts [*see Warnings and Precautions (5.3)*].

In settings such as in neonates with known or suspected exposure to maternal opioid use, where it may be preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of an alternate naloxone-containing product that can be dosed according to weight and titrated to effect.

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 NARCAN Nasal Spray.

## 2 METHODS AND MATERIALS

### 2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

<b>Table 2. FAERS Search Strategy*</b>	
Date of search	November 20, 2018
Time period of search	November 18, 2014 <sup>†</sup> - November 19, 2018
Search type	Quick Query
Product terms	Product active ingredient: naloxone, naloxone hydrochloride NDA 208411
MedDRA search terms (Version 21.1)	All adverse events
Reporter narrative	Kit OR atomiz OR nasal OR spray OR device <sup>‡</sup>
Administration route	Nasal

**Table 2. FAERS Search Strategy\***

\* See Appendix B for a description of the FAERS database.

† One year prior to approval date of pediatric labeling of Narcan (naloxone) nasal spray

‡ Terms used to identify reports of Narcan (naloxone) nasal route of administration

**3 RESULTS****3.1 FAERS****3.1.1 Total Number of FAERS Reports by Age**

Table 3 presents the number of adult and pediatric FAERS reports from November 18, 2014 to November 19, 2018 with Narcan (naloxone) nasal spray.

**Table 3. Total Adult and Pediatric FAERS Reports\* Received by FDA from November 18, 2014 to November 19, 2018 with Narcan Nasal Spray**

	All reports (U.S.)	Serious <sup>†</sup> (U.S.)	Death (U.S.)
Adults ( $\geq 17$ years)	207 (201)	63 (57)	15 (13)
Pediatrics (0 - <17 years)	1 (1)	0 (0)	0 (0)

\* 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.

**3.1.2 Selection of Pediatric Cases in FAERS (N=0)**

Our FAERS search retrieved one non-serious pediatric case from November 18, 2014 to November 19, 2018. However, this report did not report an adverse event. There were no pediatric serious adverse event cases identified during this time period.

**3.1.3 Summary of Fatal Pediatric Cases (N=0)**

We did not identify any fatal pediatric adverse event cases.

**4 DISCUSSION**

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths reported in the pediatric patient population with Narcan (naloxone) nasal spray.

**5 CONCLUSION**

DPV did not identify any pediatric safety concerns for Narcan (naloxone) nasal spray 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 Narcan (naloxone) nasal spray.

## 7 REFERENCES

1. Naloxone Hydrochloride Injection [Prescribing Information]. Lake Forest, IL: Hospira, Inc. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8535cc84-ad4a-4d67-8480-fb5a2e3406f8> February 14, 2018. Accessed December 3, 2018.
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3. Hertz S. FDA Narcan Nasal Spray NDA (#208411) Approval Letter. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2015/208411Orig1s000ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/208411Orig1s000ltr.pdf). November 18, 2015. Accessed January 7, 2019.
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## 8 APPENDICES

### 8.1 APPENDIX A. LIST OF FDA APPROVED AND MARKETED GENERIC NALOXONE INJECTION PRODUCTS

<b>Application No.</b>	<b>Strength</b>	<b>Manufacturer</b>	<b>Approval Year</b>
ANDA 070299	0.4 mg/ml	West-Ward	1985
ANDA 070172	0.4 mg/ml	Hospira	1986
ANDA 070256	0.4 mg/ml vial	Hospira	1987
ANDA 070257	0.4 mg/ml multi-dose vial	Hospira	1987
ANDA 072076	1 mg/ml	International Medication Systems	1988
ANDA 204997	0.4 mg/ml	Mylan Institutional	2014
ANDA 205014	0.4 mg/ml	Mylan Institutional	2016
ANDA 207633	0.4 mg/ml	Somerset Therapeutics	2017
ANDA 207634	0.4 mg/ml	Somerset Therapeutics	2017
ANDA 208871	0.4 mg/ml	Akorn	2017
ANDA 208872	0.4 mg/ml	Akorn	2017
ANDA 207846	0.4 mg/ml	Renaissance SSA	2018

## 8.2 APPENDIX B. 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.

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