EMERGENT®

Briefing Document
Joint Meeting of the Nonprescription Drug and the Anesthetic and Analgesic Drug Products Advisory Committees

Topic: Rx-to-OTC switch for NARCAN® (naloxone HCl) Nasal Spray 4 mg
NDA 208411

Meeting Date: February 15, 2023

Advisory Committee Briefing Materials: Available for Public Release

List of Abbreviations

BA	bioavailability
CA	Canada
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CONFER	Comprehension for Over-the-Counter Naloxone for Emergency Response
DFL	Drug Facts Label
EMS	emergency medical services
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FR	Federal Register
GCS	Glasgow Coma Scale
HCl	hydrochloride
HF	human factors
ICSR	individual case study report
IM	intramuscular
IN	intranasal
ISS	Integrated Summary of Safety
IV	intravenous
LB	lower bound
LC	labeling comprehension
LL	lower limit
LOE	lack of effect
MedDRA	Medical Dictionary for Regulatory Affairs
mg	milligram(s)
NAL	naloxone access laws
NDA	New Drug Application
OEND	Overdose Education and Naloxone Distribution
ORO	opioid-related overdose
OTC	over the counter
PBRER	Periodic Benefit-Risk Evaluation Report
PK	pharmacokinetic
PT	preferred term
PV	pharmacovigilance
REALM	Rapid Estimate of Adult Literacy in Medicine test
RR	respiratory rates
Rx	prescription

SAE	serious adverse event
SC	subcutaneous
sNDA	supplemental New Drug Application
SOC	system organ class
SUD	Substance Use Disorder
THN	take-home naloxone
Tmax	time to peak plasma concentration
UL	upper limit
US	United States
USPI	United States Prescribing Information
WHO	World Health Organization

Table of Contents

LIST OF ABBREVIATIONS 2
TABLE OF CONTENTS 4
LIST OF APPENDICES 5
1 EXECUTIVE SUMMARY 7
1.1 OTC Nasal Naloxone Addresses an Unmet Medical Need 8
1.2 Description of OTC NARCAN 9
1.3 Overview of OTC NARCAN Development Program 10
1.4 Measures to Support OTC NARCAN 11
1.5 NARCAN Meets all Key Criteria for an OTC Switch Candidate 11
1.6 Benefit-Risk Considerations for OTC Nasal Naloxone 13
2 RATIONALE FOR OTC NARCAN 13
2.1 Unmet Medical Need for OTC Nasal Naloxone 13
2.2 Factors that May Impede Access to Prescription Naloxone Products 14
2.3 The FDA's Call to Action: Expanding Access to Naloxone Through the Switch of Certain Naloxone Products from Prescription to OTC 15
2.4 Broader Access to Nasal Naloxone is Critical to Help Save Lives 16
3 THE OTC NASAL NALOXONE DEVELOPMENT PROGRAM 17
3.1 FDA's Labeling Comprehension Study 19
3.2 Human Factors Study 20
3.2.1 Methodology 20
3.3 Study Endpoints 23
3.3.1 Summary of Human Factors Results 24
3.4 Improvements to the NARCAN DFL 28
3.4.1 Conclusion 32
4 OTC NARCAN, USER INTERFACE AND REAL WORLD POST-MARKETING DATA 32
4.1 Description of OTC NARCAN Nasal Spray 32
4.2 Description of Device User Interface 33
4.3 Real-World Post-Marketing Data Supports Layperson Usage 34
4.4 Post-Marketing Safety Surveillance 36
5 OPTIMIZING OTC NARCAN ACCESSIBILITY AND EXPANDING AWARENESS 37
6 BENEFIT-RISK ASSESSMENT OF OTC NARCAN 38
6.1 Medical Need for OTC Nasal Naloxone 38

6.2 Overdose Education and Naloxone Distribution (OEND) Reduce Overdose Deaths....39
6.3 Special Considerations: Abuse/Misuse and Drug Risk Behaviour....40
6.4 OTC NARCAN has a Favorable Benefit-Risk Profile....41
7 SUMMARY AND CONCLUSIONS....41
8 REFERENCES....44

List of Appendices

APPENDIX I CURRENT PRESCRIPTION NARCAN LABELING
APPENDIX II SUMMARY OF NARCAN PHARMACOLOGY, EFFICACY, AND SAFETY
APPENDIX III SUPPLEMENTAL HUMAN FACTORS INFORMATION

LIST OF TABLES

Table 1 NARCAN Meets OTC Criteria....12
Table 2 Comparison Table of Differences Between Step 2 of FDA Model IN DFL and Proposed NARCAN DFL....19
Table 3 Primary Endpoints and Target Performance Standards....24
Table 4 Results for Human Factors Study....25
Table 5 Comparison Table of Mock OTC DFL & Carton used in Human Factors Study Compared to the Proposed Intend-to-Market (Final Proposed) Narcan DFL & Carton....29
Table 6 Medication Errors Observed for NARCAN Nasal Spray–Cumulative....35
Table 7 Device Failures Observed for NARCAN Nasal Spray - Cumulative....36
Table 8 Mean Pharmacokinetic Parameters (CV%) for Naloxone Following NARCAN (Naloxone HCl) Nasal Spray and Intramuscular Injection of Naloxone HCl to Healthy Subjects....50
Table 9 Common Events by System Organ Class (≥ 2%) – Categorized by Age Groups....57
Table 10 Common Adverse Events (>2%) – by Age Group....58
Table 11 Serious Events by SOC and PT by Age Group....63

LIST OF FIGURES

Figure 1 FDA Model IN DFL 18
Figure 2 Mock NARCAN OTC Carton Tested in Human Factors Study....20
Figure 3 Intend-to-Market (Final Proposed) NARCAN DFL....28
Figure 4 NARCAN Nasal Spray and How Used 34
Figure 5 Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection 51

1 EXECUTIVE SUMMARY

This briefing document was developed to support the February 15, 2023 Joint Meeting of the Nonprescription Drug and the Anesthetic and Analgesic Drug Products Advisory Committees, during which Emergent's supplemental New Drug Application (sNDA) for NARCAN® (naloxone HCl) Nasal Spray 4 mg will be discussed.

The document begins with an executive summary of key information, followed by a high-level review of the United States (US) opioid public health crisis and the unmet medical need for an over-the-counter (OTC) nasal naloxone product to treat opioid overdose. Also included is a review of the program to develop NARCAN OTC labeling, results from human factors (HF) testing, an outline of Emergent's efforts that will provide ongoing support to OTC consumers, patients, caregivers, and healthcare professionals, and lastly a benefit-risk analysis.

Naloxone is available as a prescription (Rx) drug in several strengths, dosage forms and routes of administration. Naloxone hydrochloride (HCl) injection (NDA 016636) was first approved by the US Food and Drug Administration (FDA) in 1971 and has been used for more than 50 years by emergency medical services (EMS) personnel or hospital emergency rooms to reverse opioid overdose and resuscitate persons who may have otherwise died. Naloxone competes for *mu* opioid receptors in the central nervous system, displacing agonist actions from opioids and reversing the effects of respiratory depression and sedation. As drug overdose deaths became the leading cause of injury death in the US (CDC, 2022), there was a need for the availability of a lay user-friendly naloxone product for use in the community setting to facilitate earlier intervention (use of naloxone) in emergency situations.

On April 3, 2014, the FDA approved the first take-home naloxone (THN) product, Evzio® (naloxone HCl) auto-injector for use by family members or caregivers to treat a person known or suspected to have had an opioid overdose. On November 18, 2015, the FDA approved the first THN (intranasal (IN) product, NARCAN® Nasal Spray (NDA 208411)) with the same indication, to reverse opioid induced respiratory depression in the emergency setting of suspected opioid overdose.

Based in Gaithersburg, Maryland, Emergent is a global life sciences company whose mission is to protect and enhance life. Dedicated to developing, manufacturing and delivering protections against public health threats, Emergent is a leader in combatting the opioid overdose epidemic as the license holder of NARCAN in the US and Canada (CA). Emergent has submitted a supplemental New Drug Application (sNDA) 208411/S-006 under section 505(b)-(2) of the Federal Food, Drug and Cosmetic Act to support the OTC approval of NARCAN Nasal Spray 4 mg.

Broadening access to nasal naloxone by switching from Rx to OTC status has been deemed by FDA (Office of the Federal Register, National Archives and Records Administration. 2022, November 15. 87 FR 68702) and other stakeholders to be critical to help respond to the current opioid epidemic – as the majority of opioid deaths occur in the community setting (Mattson et al., 2018). A key aspect of nasal naloxone's impact is its availability and rapid deployment in the setting where it is needed. Potential barriers to access may limit its impact.

There is overwhelming evidence that naloxone is both safe and effective for its intended use. Evidence from HF testing of the OTC NARCAN product label (Drug Facts Label, (DFL)) and the extensive real-world experience with the existing prescription NARCAN, demonstrate nasal naloxone can be safely and effectively used in the OTC setting.

1.1 OTC Nasal Naloxone Addresses an Unmet Medical Need

Opioid overdose and opioid induced respiratory depression are significant life-threatening conditions, and as a critical public health issue in the US, have been the focus of government and private initiatives. The Centers for Disease Control and Prevention (CDC) has reported that nearly one million people have died from a drug overdose in the US since the Agency began collecting such data in 1999, and that this number is primarily driven by opioid overdoses (CDC, 2022).

According to data from CDC, an estimated 100,306 drug overdose deaths occurred in a 12 month period ending in April 2021, which equated to an increase of 28.5% compared to the same timeframe a year before (CDC, 2021). Furthermore, recent provisional data from CDC included an estimated 107,622 drug overdose deaths in the US during 2021, a nearly 15% increase from the 93,655 deaths that were reported to have occurred in the US in 2020 (CDC, 2022)

NARCAN, as it is currently distributed and since it was first marketed in 2016, has been specifically designed for community use. It is currently being used by lay-persons typically with no formal training. It is available in all 50 states and the District of Columbia via standing orders; however, widespread access is limited by varying levels of public awareness and understanding of how to access naloxone through this mechanism exist. In addition, whilst NARCAN can be obtained by a patient or caregiver from a pharmacy without a prescription, lack of awareness of standing order policies and stigma may prevent people from obtaining naloxone from the pharmacy (Meyerson et al., 2018; Stone et al., 2020; Graves et al., 2019; Sisson et al., 2019; Thompson et al., 2019). Switching naloxone to OTC has been postulated as a solution to help mitigate some of these barriers and expand uptake and awareness for those who need it (Evoy et al., 2021). Stakeholders have advocated that a formal switch to OTC status would reduce stigma and would help facilitate widespread use of naloxone in an opioid emergency situation.

On November 15, 2022 the FDA announced that "It is our preliminary opinion at this time that naloxone HCl nasal spray up to 4 milligrams (mg), and naloxone HCl auto-injector for intramuscular (IM) or subcutaneous (SC) use up to 2 mg, have the potential to be safe and effective for use as directed in non-prescription drug labeling without the supervision of a healthcare practitioner." (Office of the Federal Register, National Archives and Records Administration. 2022, November 15. 87 FR 68702). Further the FDA stated that "although the analyses show an increased number of prescriptions dispensed from retail pharmacies and an overall increase in naloxone sales over the past five years, the increases in overdose deaths reflect a need for increased access and availability of naloxone products particularly for non-healthcare settings."

Consistent with the FDA's current thinking and approach to increasing layperson access to naloxone products, Emergent is committed in its mission to protect and enhance life and is seeking approval of OTC status of NARCAN.

1.2 Description of OTC NARCAN

OTC NARCAN is identical to prescription NARCAN (see Appendix I for the current approved prescription United States Prescribing Information (USPI) with respect to IN delivery, dosage, formulation, product quality, active pharmaceutical ingredient, drug delivery device, blister packaging and carton size. In addition, OTC NARCAN is proposed to have the same indication as the prescription product, which includes both the adult and pediatric populations:

- Is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
- Intended for the immediate administration as emergency therapy in settings where opioids may be present.
- Not a substitute for emergency medical care.

The active pharmaceutical ingredient is naloxone HCl (naloxone). Naloxone HCl is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists.

NARCAN is for IN use only. The product delivers 4 mg naloxone HCl per spray. It is supplied as a single 4 mg dose of naloxone HCl in a 0.1 mL pre-filled IN spray (see Figure 4) and in a carton containing two nasal spray devices in the event repeat dosing is needed. No additional device assembly or priming is required.

NARCAN is stored at room temperature and has a 3-year shelf-life.

Initial dosing of nasal naloxone in adults and pediatric patients is one spray delivered by IN administration, which delivers 4 mg of naloxone HCl. Repeat dosing for adults and pediatrics is the same as the current prescription nasal naloxone. Additional doses of nasal naloxone can be administered to adults and pediatrics, using a repeat nasal spray following the initial dose. If the patient does not respond or responds and then relapses into respiratory depression, additional doses of nasal naloxone may be given every 2 to 3 minutes until emergency medical assistance arrives.

When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

The initial prescription (Rx) approval of NARCAN is supported by the efficacy of the approved IM naloxone HCl (Narcan for injection, NDA 016636) in addition to literature (see Appendix II, Section 1.2).

To support the approval of NARCAN, one pivotal comparative PK bioavailability (BA) study (Naloxone-Ph1a-002) was conducted in the original NDA for NARCAN (NDA 208411) (see Appendix II, Section 1.1.1). This study was conducted in 30 healthy volunteers and concluded that NARCAN can deliver a dose of naloxone IN that is approximately 50% bioavailable to IM. As such, a 4 mg IN dose will provide a dose that is equivalent to the most common IM dose of 2 mg injected. The time to peak plasma concentration (t_{max}) is approximately the same as injectable naloxone (2 mg) indicating that time to onset will be similar.

The safety profile of nasal naloxone has been well established, with more than six years of post-marketing safety data and, as per the current cumulative Periodic Benefit-Risk Evaluation Report (PBRER) reporting period (to 02 OCT 2022), with approximately 44 million doses (devices) distributed in the US and CA (NARCAN was licensed in CA in 2016). Post-marketing safety data has been monitored closely during this time. Nasal naloxone is intended to be administered by a layperson to a non-responsive individual. It has a relatively low risk profile, is easy to use in emergency situations with no formal training, has no needle-stick injury risk and provides a consistent concentration of naloxone in each dose. There is no risk of overdose, making it appropriate for effective layperson usage which has been demonstrated since its launch. NARCAN is currently approved for use in the community setting, and this will not change should NARCAN become available as an OTC product. From market authorization to 02OCT2022 (the current cumulative PBRER reporting period), cases of medication error and other product user errors for NARCAN are minimal (relative frequency 0.28 per 100,000 dose (NARCAN Nasal Spray Periodic Benefit-Risk Evaluation Report (Approved December 2022)). Device failure is also reported infrequently (relative frequency 0.03 per 100,000 doses). This latest PBRER data aligns with that previously reported in the safety analysis that was included in the sNDA submission (see Appendix II, Section 1.4).

1.3 Overview of OTC NARCAN Development Program

The important issue for the OTC switch for NARCAN, is that the product can be safely and effectively used without healthcare intervention guided solely by the product label or DFL. Real-world experience supports that healthcare professional supervision is not required for safe and effective use. In fact, NARCAN was specifically designed for community-use and is used by lay-persons with no specific training. A conversion in the market status from Rx to OTC will not change the intended use nor use environment for nasal naloxone. Further real-world post-marketing evidence in support of the intended use is provided in Section 4.3.

In its own efforts to meet the urgent public health need for expanded access to naloxone, the FDA developed and tested a model IN naloxone DFL. Their testing of this label concluded that naloxone can be used appropriately by consumers and guided entirely by the DFL (published by FDA 17 January 2019, Comprehension for Over the Counter Naloxone for Emergency Response, '(CONFER)' study).

The following additional activities have been conducted by Emergent to support the switch of nasal naloxone from Rx to OTC:

- Emergent developed a NARCAN-specific DFL. The DFL was a reproduction of the FDA-developed model IN naloxone DFL, with minimal additions to include product-specific information and directions (see Table 3 and Figure 2).
- Emergent conducted a HF study to evaluate the effectiveness of the proposed NARCAN-specific DFL. To confirm its ability to guide appropriate use, testing included users from various backgrounds, including low literacy level and adolescents. Testing confirmed the product can be used safely and effectively, in the OTC setting, including low literacy and adolescent subjects (see Section 3.2).
- A comprehensive review of safety was performed (see Appendix II, Section 1.3), including analysis of post-marketing safety data from an FDA database and international databases (cumulative safety data from November 2015- June 2021). To date, there have been no new safety signals identified since market authorization. This includes findings specific to the target population and the route of administration. The Benefit-Risk profile remains positive and supports OTC availability.

1.4 Measures to Support OTC NARCAN

Emergent has a multi-pronged, extensive approach to support the OTC NARCAN offering, including education programs (product use/training), advancing consumer awareness (website, digital, traditional advertising), communications and advocacy.

Emergent advocates for programs, initiatives, and solutions that further strengthen and expand access to potentially lifesaving opioid overdose reversal medications for those who need them. Emergent is proud of its long-standing history of working with Federal and state governments, community organizations, healthcare practitioners and public health officials to educate people who may be at risk of an opioid overdose. We will continue to work toward wide and equitable access to naloxone for those who need it.

As it does currently, Emergent will continue to monitor safety data of OTC NARCAN, collecting data received from any source including consumers, healthcare professionals, product inquiries, complaints and scientific literature. Safety signals are reviewed by the Emergent Pharmacovigilance (PV) department in accordance with Emergent standard procedures and postmarket safety reporting is performed per regulatory reporting requirements for PV.

1.5 NARCAN Meets all Key Criteria for an OTC Switch Candidate

As numerous medicinal products have made the transition from prescription to OTC status, a series of generalizable principles have evolved and been accepted as key properties in determining "switchability" or "OTCness". Table 1 outlines these criteria, how NARCAN meets these criteria, and its appropriateness for OTC availability.

Table 1 NARCAN Meets OTC Criteria

OTC CRITERIA	NARCAN	OTC CRITERIA MET (YES/NO)
User must be able to self-diagnose	Per FDA approved USPI (see Appendix I), NARCAN can be used in cases of suspected or known opioid overdose. The product is administered by a layperson to a non-responsive individual	YES
Product is adequately labeled to drive correct use by the consumer	The NARCAN DFL has been tested in a Human Factors study (see Section 3.2). Testing demonstrated that the product could be used safely and effectively without healthcare intervention and guided solely by the DFL. FDA's comprehension studies of the model IN naloxone DFL, which is nearly identical to the Narcan DFL with the primary exception being Step 2, or how to give a dose of NARCAN, demonstrated that the DFL content is well understood by consumers of all ages, literacy levels, and backgrounds. Real-world post-marketing data from Rx NARCAN, which is currently used by lay persons, indicates that there is minimal misuse of the product (see Section 4.3)	YES
Benefits of increased access outweigh potential risks	NARCAN has a well-established safety and efficacy profile (Appendix II). The potential life-saving benefits of administering nasal naloxone outweigh the risks of failure to reverse overdose when used with other appropriate measures (e.g., calling 911) (see Section 6.4).	YES
Low potential for misuse and abuse	There is no evidence that the broader availability of nasal naloxone would have consequences with respect to enhancing more risky behavior with respect to drug use. Experience with use in the community setting has not demonstrated any additional risks (see Section 6.3). Real-world data from Rx NARCAN, which is currently used by lay persons, indicates minimal misuse (see Section 4.3 for details).	YES
Health practitioners are not needed for the safe and effective use of product	Prescription NARCAN has been specifically designed for community use. It is currently used by lay persons in the absence of the health practitioner (see Section 4.3)	YES

Reversal of a suspected opioid overdose is a new indication for an OTC product. The NARCAN OTC switch differs significantly from most Rx-to-OTC switch categories, which have been focused on self diagnosable symptom management, because it's an emergency use product intended to be used by a layperson bystander on a non-responsive individual. It can

be readily demonstrated that NARCAN measures up to all OTC criteria and is a suitable candidate for OTC status, as supported by the real-world data from the established prescription NARCAN. This, coupled with broader access, make a timely approval of OTC status warranted.

1.6 Benefit-Risk Considerations for OTC Nasal Naloxone

NARCAN has been marketed in the US since February 16, 2016 and in CA since October 3, 2016; since this time, the distribution (US and CA) of NARCAN is estimated to be approximately 44 million doses (devices). NARCAN has a proven benefit-risk profile with a wealth of post-marketing experience. The safety and efficacy findings for NARCAN in community-use settings, support the clinical benefit of the product. NARCAN can help save lives.

- NARCAN has a relatively low risk profile and has a rapid response time (Krieter, 2016)
- It is easy to use in emergency situations, inhalation is not required, requires no assembly or specialized training, is light to carry, and is needle-free (no needle-stick injury risk)
- It can be easily carried and stored in the home or community setting
- NARCAN provides a consistent concentration of naloxone in each dose that has been demonstrated to be safe and effective

Naloxone, the active pharmaceutical ingredient of NARCAN, is not a controlled substance and has no known abuse potential.

In the presence of physical dependence on opioids, naloxone will produce withdrawal symptoms, which may appear within minutes of naloxone administration and will subside in about 2 hours (refer to Appendix I, Section 5.3 “Precipitation of Severe Opioid Withdrawal). Educational material will guide caregivers on how to recognize the signs and symptoms of opioid withdrawal.

Real-world post-marketing data indicates minimal misuse potential (see Section 4.3).

The favorable benefit-risk profile of NARCAN will remain unchanged in the switch to OTC. Expanding access to OTC NARCAN beyond the current distribution methods, will help remove barriers to access and allow anyone to be administered naloxone rapidly, by a layperson, providing timely access to a potentially life-saving medicine until emergency services arrive.

2 RATIONALE FOR OTC NARCAN

2.1 Unmet Medical Need for OTC Nasal Naloxone

Opioid overdose and opioid induced respiratory depression are significant life-threatening conditions, and as a critical public health issue in the US, have been the focus of government

and private initiatives. The Centers for Disease Control and Prevention (CDC) has reported that nearly one million people have died from a drug overdose in the US since the Agency began collecting such data in 1999, and that this number is primarily driven by opioid overdoses (CDC, 2021).

According to data from CDC, an estimated 100,306 drug overdose deaths occurred in a 12 month period ending in April 2021, which equated to an increase of 28.5% compared to the same timeframe a year before (CDC, 2021). Furthermore, recent provisional data from CDC included an estimated 107,622 drug overdose deaths in the US during 2021, a nearly 15% increase from the 93, 655 deaths that were reported to have occurred in the US in 2020 (CDC, 2022)

Naloxone is available as a prescription drug in several strengths, dosage forms and routes of administration. Naloxone HCl injection (NDA 016636) has been approved by FDA and used for more than 50 years by EMS personnel or hospital emergency rooms to reverse opioid overdose and resuscitate persons who may have otherwise died. However, as drug overdose deaths became the leading cause of injury death in the US (CDC, 2022), the need arose for the availability of a more lay user-friendly naloxone product for use in the community setting to facilitate earlier intervention (use of naloxone) in emergency situations.

On April 3, 2014, the FDA approved the first THN product, Evzio® (naloxone HCl) auto-injector for use by family members or caregivers to treat a person known or suspected to have had an opioid overdose. On November 18, 2015, the FDA approved the first THN (intranasal) product, NARCAN® Nasal Spray with the same indication.

Subsequent to the approval of the first two THN products, in 2021 the FDA has approved Kloxxado® (8 mg intranasal spray), Zimhi® (5 mg intramuscular pre-filled syringe), as well as Teva's and Padagis's generic naloxone nasal spray 4 mg.

There are, however, no naloxone products currently approved by FDA for OTC use, and although several naloxone products are available for use in the community setting, there remain potential barriers to access, as outlined below in Section 2.2.

2.2 Factors that May Impede Access to Prescription Naloxone Products

Several naloxone products are available for use in the community setting (including nasal naloxone), and all 50 states and the District of Columbia have policies in place to help improve access to naloxone, by allowing individuals to buy naloxone at the pharmacy without a prescription. However, many stakeholders, including the FDA have concluded that the prescription (Rx) status of these critical, emergency use products continue to be a potential barrier to access. The current level of naloxone distribution does not match the number of at-risk patients, and despite recommendations, co-prescribing of naloxone to patients at increased risk of overdose remains infrequent (Evoy et al., 2021).

Negative personal experiences and fear of provider stigma may cause people with Substance Use Disorder (SUD) to delay or avoid engagement with the healthcare system. Concerns may prevent individuals from discussing their drug use, requesting a naloxone prescription, or returning to request additional supplies if they use the naloxone (Meyerson et al., 2018;

Stone et al., 2020; Graves et al., 2019; Sisson et al., 2019; Thompson et al., 2019). Switching naloxone to OTC has been postulated as a pathway to help mitigate some of these barriers and expand uptake among opioid users (Evoy et al., 2021).

To help address these barriers, states have implemented naloxone access laws (NALs) aimed at increasing access to naloxone in the community. All 50 states have some type of naloxone access laws (standing orders, co-prescribing laws etc.). However, the current NAL approach has led to confusion, particularly given the variability in state-level NALs and nuances of implementation (Evoy et al., 2021). In the experience of Evoy et al., 2021, misconceptions regarding the status of naloxone are often present even among healthcare professionals and public health decision-makers. Converting nasal naloxone to OTC status may reduce the confusion that currently surrounds the proper methods for accessing and distributing it.

Prescription NARCAN can also be purchased in bulk quantities by police, EMS, harm reduction groups, or any other organization directly from Emergent. Due to the Rx status of NARCAN, Emergent is required to receive a doctor's signature to fulfil the order. Furthermore, any organization looking to purchase NARCAN must have an address that is not a private home to receive shipments, proof of a medical or pharmacy license, and the ability to comply with state and Federal regulations for storage and distribution.

Lastly, naloxone is unique from other Rx drugs in that it is an emergency treatment for the reversal of overdose, and therefore, unlikely to be self-administered. Given this, there are potential scenarios where the product is administered by someone other than the person for whom it was prescribed. Due to concerns over liability, prescribers may be reluctant to prescribe naloxone to a third party (Office of the Federal Register, National Archives and Records Administration. 2022, November 15. 87 FR 68702).

2.3 The FDA's Call to Action: Expanding Access to Naloxone Through the Switch of Certain Naloxone Products from Prescription to OTC

In the wake of the opioid epidemic, the FDA has undertaken extensive efforts to support the development of OTC naloxone and to make naloxone more readily available and more accessible to help reduce opioid deaths. Amongst these efforts, on January 17, 2019, the FDA announced that it had taken the unprecedented step to develop a model DFL. To encourage companies to enter the OTC market and increase access to naloxone, the FDA developed this model DFL with easy-to understand pictograms on how to use the drug and label comprehension testing to ensure the instructions were simple to follow.

More recently, on November 15, 2022, the FDA issued a Federal Register Notice (FR 68702) (Office of the Federal Register, National Archives and Records Administration. 2022, November 15. 87 FR 68702), in which the FDA announced that it had made a preliminary assessment that naloxone products may be approvable as safe and effective for non-prescription use for the naloxone HCl nasal spray up to 4 mg and naloxone HCl, autoinjector for IM or SC use up to 2 mg. In this FR 68702 notice, the FDA indicated that they believe that "the prescription requirements for certain naloxone products may not be necessary for the protection of the public health" and further state that "…these naloxone products have the

potential to be safe and effective for use as directed in nonprescription drug labeling without the supervision of a healthcare practitioner".

Per FR 68702, current evidence suggests that "increasing access to naloxone has the potential to reduce opioid overdose deaths (Wheeler, 2014, Doe-Simkins, 2014, Rowe, 2015, Walley, 2013).

The approval of OTC nasal naloxone would align with FDA's goals to combat the opioid overdose crisis.

2.4 Broader Access to Nasal Naloxone is Critical to Help Save Lives

Changing NARCAN's market status from prescription to OTC is expected to support broader access to those at risk of an opioid overdose and can help save lives. The key to its effectiveness is its availability and rapid deployment in the setting where it is needed, in the community. In the event of a life-threatening opioid-related overdose (ORO), there is a relatively short window of time in which naloxone can be administered to effectively reverse the overdose Therefore, increasing naloxone access in the community, particularly among those closely associated with persons at elevated overdose risk, is a crucial step to reducing ORO mortality as such measures increase the likelihood of timely naloxone administration (Evoy et al., 2021).

NARCAN, as an OTC treatment option for opioid overdose, has a favorable benefit-risk profile:

Established efficacy: NARCAN efficacy is supported by the efficacy of the approved IM naloxone HCl (NDA 011636), originally licensed by FDA in 1971 (see Appendix II, Section 1.2) and IN formulation (NDA 208411, approved on November 18, 2015). Nasal naloxone is designed to be used in a non-medical, community setting. It is administered as a fixed and efficacious dose thereby ensuring that the optimal initial dose is administered as quickly as possible

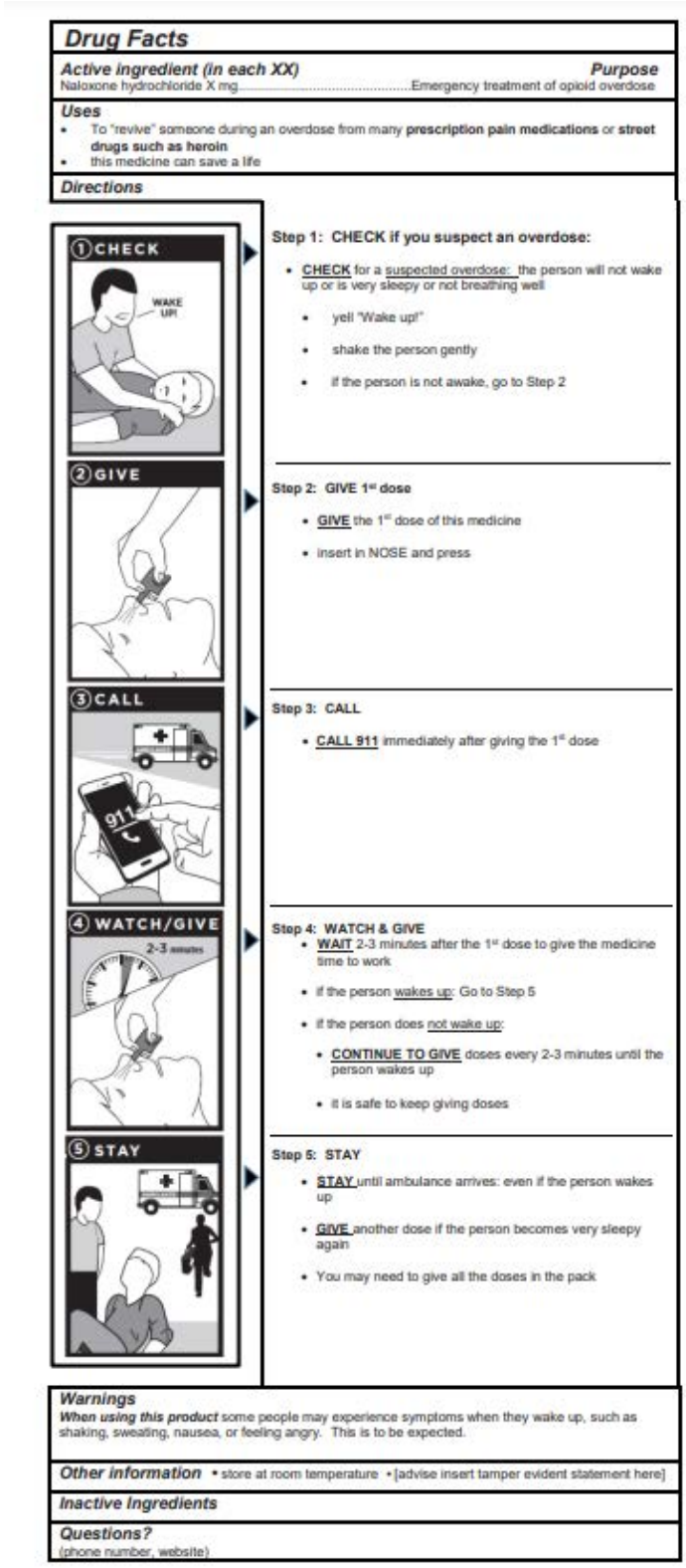
Easy to administer by lay-persons: Since its launch in 2016, NARCAN has been administered effectively by lay-persons to non-responsive individuals in instances of opioid overdose or suspected opioid overdose. Minimal to no training is required to administer nasal naloxone. Current community-based programs provide naloxone, without patient-based prescriptions and in settings where nasal naloxone is administered without a medical intermediary.

Well-characterized, favorable safety profile: Nasal naloxone has a well-established safety profile. Extensive analysis of safety databases and scientific literature reveal that there are no new safety risks from the marketed use of nasal naloxone. Real-world post-marketing data demonstrates that reports of misuse are minimal (see Section 4.3). No additional risks have been suggested relative to OTC availability.

3 THE OTC NASAL NALOXONE DEVELOPMENT PROGRAM

To leverage the learnings from FDA's label research, Emergent chose to adopt FDA's model IN naloxone DFL (refer to Figure 1).

Figure 1 FDA Model IN DFL



The only product-specific modifications to the DFL are in Step 2 of the directions (how to administer NARCAN). The differences between Step 2 of the DFL are outlined in Table 2.

Table 2 Comparison Table of Differences Between Step 2 of FDA Model IN DFL and Proposed NARCAN DFL

FDA Model IN DFL – Step 2	Proposed NARCAN DFL - Step 2
Step 2: GIVE 1st dose **GIVE** the 1st dose of this medicine Insert in NOSE and press	Step 2: Give 1st dose of Narcan Nasal Spray **HOLD** the Narcan Nasal Spray with your thumb on the bottom of the plunger **INSERT** the tip of the nozzle into either NOSTRIL **PRESS** the plunger firmly to give the 1st dose

A HF validation study was conducted to evaluate the ability of potential OTC user groups to follow and apply the directions for use in Step 2 on the proposed DFL to appropriately administer nasal naloxone in a simulated opioid emergency and are reviewed below (see Section 3.2). Results demonstrate that the overall HF study was successful. These findings suggest that the proposed OTC nasal naloxone DFL would be sufficient to guide correct administration of the product by a diverse group of potential user groups in an OTC setting.

3.1 FDA's Labeling Comprehension Study

The FDA's OTC naloxone DFL was successfully tested by FDA using a standard label comprehension (LC) study design (Comprehension for Over-the-Counter Naloxone for Emergency Response, 'CONFER' study). This model DFL was developed with an accompanying pictogram that could be placed next to the DFL to correspond with the DFL directions. Of the eight primary endpoints, six met the pre-specified threshold for correct/acceptable responses. The endpoint "call 911" immediately did not meet the lower bound (LB) threshold of 90%, although it was close to the threshold (88%). The FDA's overall conclusion was that the results of the study supported the use of the tested naloxone DFL in the OTC setting and contemplated that "because naloxone is a potentially life-saving treatment, it may be reasonable to consider a LB of 88% to be acceptable. If naloxone is given and most users call 911, many lives can be saved, and this is a much better alternative than not giving naloxone at all" (published by FDA 17 January 2019, Comprehension for Over the Counter Naloxone for Emergency Response, '(CONFER)' study). The FDA further advised sponsors to consider how to improve the message to **call 911 immediately** as they developed their DFLs.

Based on initial feedback from the FDA, Emergent utilized and fully adopted the FDA model IN DFL (i.e., adopted Steps 1, 3, 4, and 5 content verbatim and implemented into existing nasal naloxone product carton), without the need for additional label comprehension studies and other DFL changes, other than specific directions for administration.

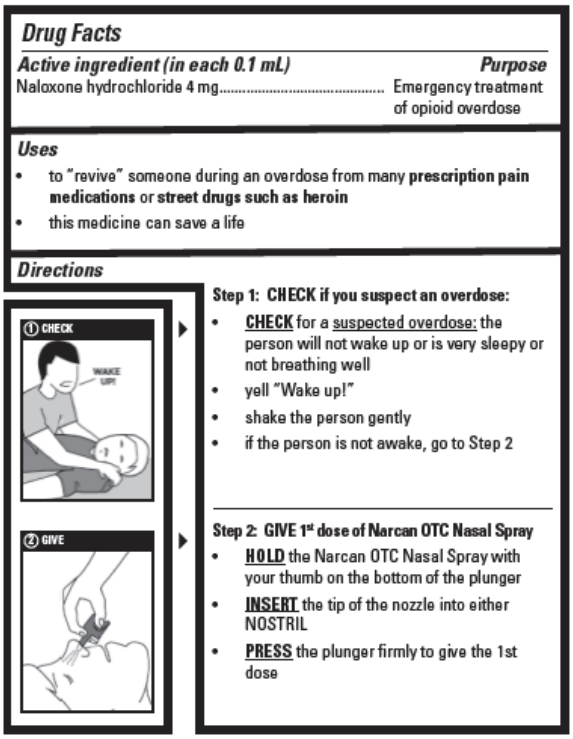
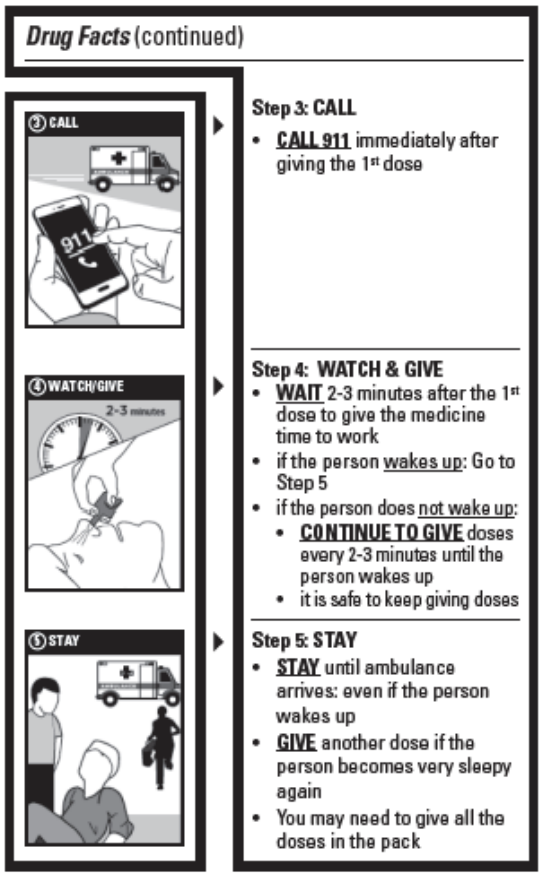
3.2 Human Factors Study

3.2.1 Methodology

This study was conducted in accordance with the FDA Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products (August 2010) and the Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (February 2016).

The NARCAN DFL that was studied in the Human Factors study is shown in Figure 2.

Figure 2 Mock NARCAN OTC Carton Tested in Human Factors Study

Right Side Panel	Back Panel
	

The primary objectives of the HF study were to evaluate those steps not currently covered by the FDA's model IN naloxone DFL and to verify that participants from all representative user groups could use the proposed DFL to appropriately administer NARCAN in a simulated overdose setting. Other than the product-specific administration directions in Step 2, the proposed DFL is adopted verbatim from the FDA model IN DFL, and therefore the HF

study focused on testing Step 2. The critical tasks listed in Step 2 on the proposed DFL, labeled as Steps 2a-2c below, represented the three Primary Endpoints of the study (Task 1, Task 2, Task 3).

Steps of the proposed DFL tested in the HF study

Note: sub-steps are numbered below and throughout for clarity but are only presented as bullet points on the DFL. The steps below reflect the tested measures, rather than the full and complete label language on the DFL which is shown in Figure 1. See Footnotes 2 and 3 below for further explanation.

Step 1: CHECK if you suspect an overdose :

Step 1a: yell "Wake up!"

Step 1b: shake the person gently[1]

Step 2: GIVE 1st dose of Narcan OTC Nasal Spray

Step 2a: HOLD the Narcan OTC Nasal Spray with your thumb on the bottom of the plunger **(Task 1)**

Step 2b: INSERT the tip of the nozzle into either nostril **(Task 2)**

Step 2c: PRESS the plunger firmly to give the 1st dose **(Task 3)**

Step 3: CALL

CALL 911 immediately after giving the 1st dose

Step 4: WATCH & GIVE[2]

CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up

Step 5: STAY

Step 5a: STAY until ambulance arrives even if the person wakes up

Step 5b: GIVE another dose if the person becomes very sleepy again

[1] The proposed DFL includes the following bulleted statement under Step 1 b "if the person is not awake, go to Step 2". This was not applicable for the HF demonstration as it was intentionally structured for the participants to assume that the person did NOT wake up, in order to be able to test the task of administering a first dose.

[2] The proposed DFL includes the following bulleted statement under Step 4 of "if the person wakes up: Go to Step 5" from the proposed DFL was not applicable per se for the HF simulation as it was intentionally structured for the participants to assume the person did NOT wake up, in order to be able to test the task of administering a second dose.

The secondary objective of this study was to evaluate the composite measure of the proportion of participants who correctly completed Primary Endpoint Tasks 2 and 3, which together represent the critical procedures in administering OTC nasal naloxone to an overdose victim: "INSERT the tip of the nozzle into either NOSTRIL" and "PRESS the plunger firmly to give the 1st dose". Note that Task 1 was not considered in this composite endpoint calculation because even if participants held the device incorrectly, they might still successfully administer an effective dose by pressing the plunger firmly in some other way.

Other steps listed in the directions for use in the proposed DFL which are not specific to NARCAN and do not represent critical tasks to administration of the drug per se. (i.e., Step 1, Step 3, Step 4 and Step 5), and were thus classified as "Other Measures" or descriptive endpoints. In addition, participant-reported responses regarding reasons for any observed incorrect HF performance behaviors were analyzed and summarized, along with information about participants' prior awareness and knowledge of naloxone, and any prior experience purchasing or administering naloxone.

The HF Study was an open-label, multicenter study with in-person, one-on-one, structured interviews. Interested respondents were first pre-screened for basic qualification criteria; those who met initial entry criteria scheduled an appointment for a brief interview to complete the Rapid Estimate of Adult Literacy in Medicine test (REALM, for those ages 18 and older) or the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen, for those under age 18). The REALM and REALM-Teen tests were administered via an audio/video interface for remote data collection to characterize participants' health literacy prior to arriving on site, to ensure adequate representation of low literacy participants in the study. After completion of the REALM or REALM Teen tests, qualified participants were scheduled for the in-person HF interview.

Once on site, participants were re-screened for inclusion / exclusion criteria, and informed consent was obtained. Participants were then presented with the proposed OTC NARCAN mock package, which displayed the DFL that was being assessed (Figure 2), and containing two actual, production-ready devices containing water. They were allowed as much time as needed to review the mock package and DFL, and then were asked by a trained interviewer to demonstrate administration of the product in a simulated overdose situation. The interviewer carefully observed participants' behaviors and classified them based on the correct or incorrect performance of each step in administering nasal naloxone as listed on the proposed DFL. Standardized label comprehension questions were then asked to assess understanding of any steps listed on the DFL that the participant failed to demonstrate or adequately verbally describe during the HF demonstration. This was to better assess if participants failed to demonstrate a step because they misunderstood the label or may have failed to demonstrate due to limitations of the simulated overdose setting or other factors.

It was planned that a minimum of 15 participants in each of the following potential consumer user groups would be interviewed, for a total of roughly 60 participants. Additionally, the target proportion of participants who read below the threshold for normal literacy based on the REALM or the REALM-Teen test (scores ≤60) was 30%, distributed among all subgroups/user groups.

The actual proportion of low literacy participants in the study population was 29.6%, after enrichment. The number of participants in each user group are listed below and are consistent with the standards for these type of studies:

1. Adult all-comers (general population), age 18 or older (n=18)
2. Adolescent general population, ages 15-17 (n=19)
3. Adult opioid users, age 18 or older (n =16)
4. Adult associates of opioid users, age 18 or older (n=18)

The primary purpose of this study was to evaluate if the product-specific nonprescription labeling elements could appropriately guide correct consumer behavior when presented with a simulated emergency overdose situation, with no prior exposure to the proposed OTC labeling or training of any kind. First responders and emergency personnel were already shown to be able to successfully administer nasal naloxone in the previous HF testing for the initial Rx approval, and thus were not included as part of this study since the device is identical to the prescription product, and it was assumed that modifications to the directions for the OTC product would not impact their understanding or ability to administer the medication.

3.3 Study Endpoints

The most essential and safety-critical procedures to measure were classified as primary endpoints to demonstrate that participants could correctly administer the product using the instructions on the proposed OTC labeling. Additionally, these procedures represent the product-specific directions for use for NARCAN modified as needed from the FDA model IN DFL. The primary endpoints of the study were to evaluate if participants could successfully perform the following product-specific dosing tasks on the proposed OTC NARCAN DFL:

Step 2: Give 1st dose of Narcan OTC Nasal Spray

1. HOLD the Narcan OTC Nasal Spray with your thumb on the bottom of the plunger
2. INSERT the tip of the nozzle into either NOSTRIL
3. PRESS the plunger firmly to give the 1st dose

Each primary endpoint was assigned a corresponding target performance standard (Table 3) based on an assessment of the clinical risk associated with inadequate performance on that critical task and was considered successful if the lower limit (LL) of the two-sided 95% Confidence Interval (CI, Wilson's Score) for the obtained correct or acceptable performance equaled or exceeded the target performance standard.

Table 3 Primary Endpoints and Target Performance Standards

Performance Endpoints	Target Performance Standard
Step 2 Give 1st dose of Narcan OTC Nasal Spray	N/A
1. HOLD the Narcan OTC Nasal Spray with your thumb on the bottom of the plunger	85%
2. INSERT the tip of the nozzle into either NOSTRIL	90%
3. PRESS the plunger firmly to give the 1st dose	90%

3.3.1 Summary of Human Factors Results

The study enrolled a diverse group of participants. Of the 71 participants, 21 (29.6%) were defined as low literacy according to the REALM or REALM-Teen test. The mean age of participants was 40.0 (SD = 18.97), with a range of 15 to 76 years of age. There were 12 participants (16.9%) that identified as Black or African American, 1 (1.4%) as Asian, 1 (1.4%) as Native Hawaiian or Other Pacific Islander, 5 (7.0%) as American Indian or Alaska Native, and 1 (1.4%) also included "Hispanic" when asked their race (which was recorded in the "other" option). There were 58 participants (81.7%) who stated their race was White. Of the 52 adult participants, 3 (4.2% of the total sample) did not have a high school diploma, 10 (14.1%) received their high school diploma or GED, and 13 (18.3%) finished some college or technical school. Eighteen of the 52 adult participants (25.4%) received a college degree and 8 (11.3%) received a post-graduate degree. Of the 19 adolescents who completed the interview and provided demographic information, the highest level of education completed at the time of the interview were as follows: 1 participant (1.4% of the total sample) completed 8th grade, 5 participants (7.0%) completed 9th grade, 11 participants (15.5%) completed 10th grade, 1 (1.4%) participant completed 11th grade, and 1 participant (1.4%) had completed some college or technical school. Hispanic participants comprised 9.9% the study population. All participants were asked if they had heard of naloxone prior to participating in the study, with 25.4% (18/71) answering affirmatively, a majority of whom were adults (17/18).

Results for the Primary Endpoints, the Secondary Endpoint and Descriptive Endpoints are summarized in Table 4.

Table 4 Results for Human Factors Study

	All Subjects (N=71) **% Correct/Acceptable** **95% CI (LL, UL)**
Primary Endpoints	
Step 2: Give 1st dose of Narcan OTC Nasal Spray Step 2a: Hold the Narcan OTC Nasal Spray with your thumb on the bottom of the plunger	Correct HF demonstration: 69/71 97.2% (90.3, 99.2)
Step 2b: Insert the tip of the nozzle into either nostril	Correct HF demonstration: 69/71 97.2% (90.3, 99.2)
Step 2c: PRESS the plunger firmly to give the 1st dose	Correct HF demonstration: 66/71 93.0% (84.6, 97.0) + Acceptable Responses to LC Follow-up: 67/71 94.4% (86.4, 97.8)
Secondary Endpoint	
The composite measure of the proportion of participants who performed both: "INSERT the tip of the nozzle into either NOSTRIL" and "PRESS the plunger firmly to give the 1st dose"	Correct HF demonstration: 66/71 93.0% (84.6, 97.0) + Acceptable Responses to LC Follow-up: 67/71 94.4% (86.4, 97.8)

	All Subjects (N=71) **% Correct/Acceptable** **95% CI (LL, UL)**
Other Measures	
Step 1: CHECK if you suspect an overdose: Step 1a: Yell "Wake up!" Step 1b: Shake the person gently	Correct HF demonstration: 61/71 85.9% (82.8, 96.1) Correct HF demonstration: 65/71 91.5% (82.8, 96.1) + Acceptable Responses to LC Follow-up: 68/71 95.8% (88.3, 98.6)
Step 3: CALL: CALL 911 Immediately after giving the 1st dose	Correct HF demonstration: 70/71 98.6% (92.4, 99.8) Correct HF demonstration: 61/71 85.9% (76.0, 92.2) + Acceptable Responses to LC Follow-up: 65/71 91.5% (82.8, 96.1)
Step 4: WATCH & GIVE: CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up	Correct HF Demonstration: 69/71 97.2% (90.3, 99.2) + Acceptable Responses to LC Follow-up: 70/71 98.6% (92.4, 99.8)

	All Subjects (N=71) **% Correct/Acceptable** **95% CI (LL, UL)**
Step 5: STAY: Step 5a: STAY until ambulance arrives even if the person wakes up Step 5b: GIVE another dose if the person becomes very sleepy again	Correct HF Demonstration: 64/71 90.1% (81.0, 95.1) + Acceptable Responses to LC Follow-up: 66/71 93.0% (84.6, 97.0) Correct HF Demonstration: 28/71 32.4% (22.7, 43.9) + Acceptable Responses to LC Follow-up: 42/71 59.2% (47.5, 69.8)

N=Number of participants, CI = Confidence Interval, LL = Lower Limit, UL = Upper Limit

The results demonstrated that the HF study was successful. The lower limit of the 95% CI exceeded the pre-defined target performance thresholds for the first and second Primary Endpoints (Step 2a and Step 2b) at 90.3% (for each). While the target performance threshold of 90% was not met for the third Primary Endpoint (Step 2c) with a lower limit of the 95% CI at 86.4%, the observed proportion of correct or acceptable performance of this step was 94.4% of subjects.

As displayed above in Table 4, five participants did not adequately demonstrate Step 2c. See Appendix III for a summary of their demographic characteristics, HF performance, and comprehension of the label direction.

Overall, the results of the HF study indicates that the instructions in the labeling of "PRESS the plunger firmly to give the 1st dose" does not introduce or increase use-related risk. Moreover, this instruction (i.e., "PRESS the plunger firmly...") is the same as that currently used in the prescription product, for which no post-marketing reports received to date indicate that these instructions are difficult to follow (from more than six years of data and approximately 44 million devices distributed). There is only one post-marketing report of "device difficult to use" (refer to Table 6 and Table 7, from more than six years of data and approximately 44 million devices distributed).

Notably, the HF study demonstrated that 98% of participants correctly demonstrated and/or understood Step 3 "CALL 911".

3.4 Improvements to the NARCAN DFL

As a result of the HF Validation Study, and for the interest of optimizing the label, several changes were made to increase readability of the DFL.

- Change in the layout of the carton panels (i.e., moving Steps 1-2 from the right side panel to the back panel, and Steps 3,4,5 from the back panel to the left side panel).
- Increasing the font size of the text above the pictograms, and
- Changing the color and background of the text above the pictograms

The intend-to-market (final proposed) DFL is shown in Figure 3. Table 5 provides a comparison table of the mock OTC DFL used in the pivotal HF Validation Study to the proposed intend-to-market carton.

Figure 3 Intend-to-Market (Final Proposed) NARCAN DFL

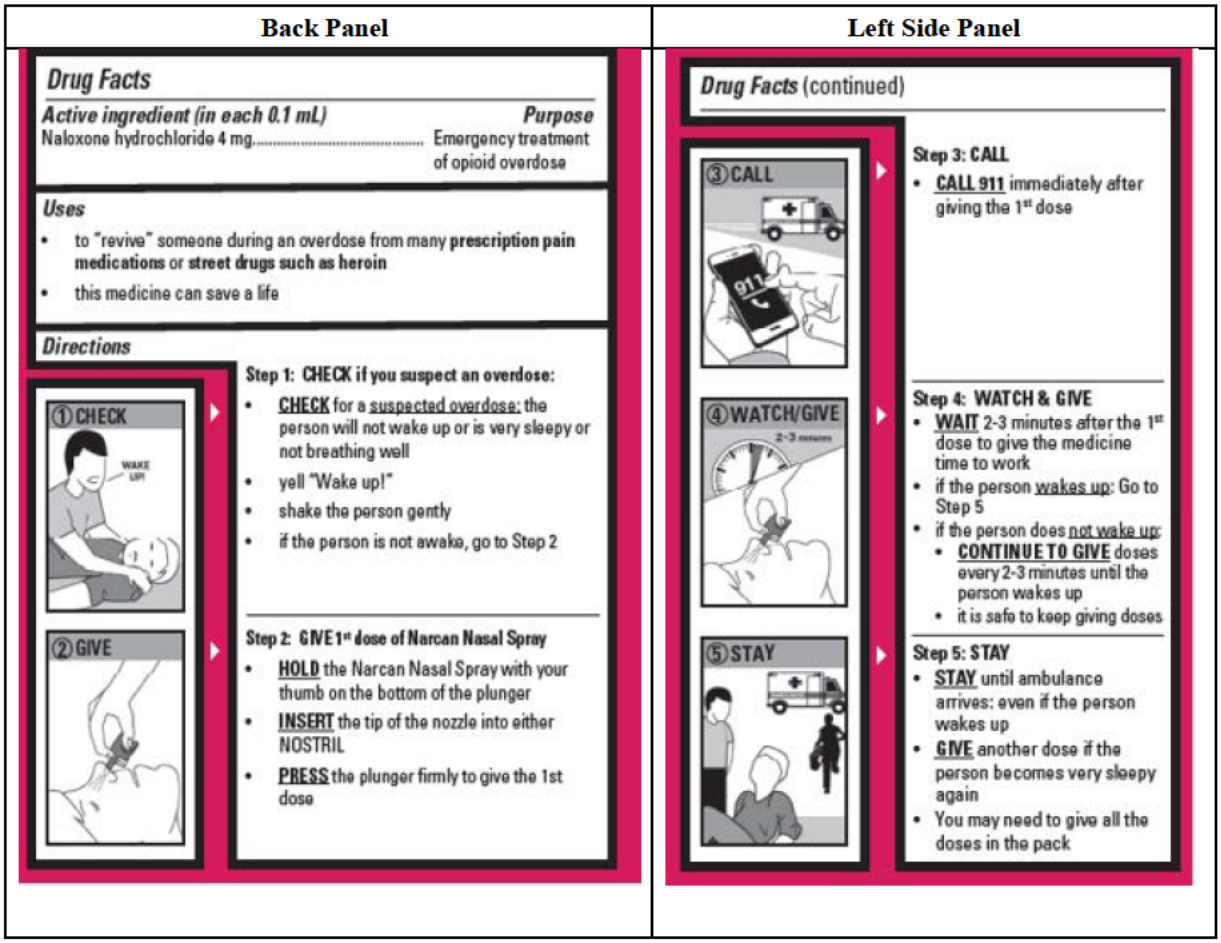
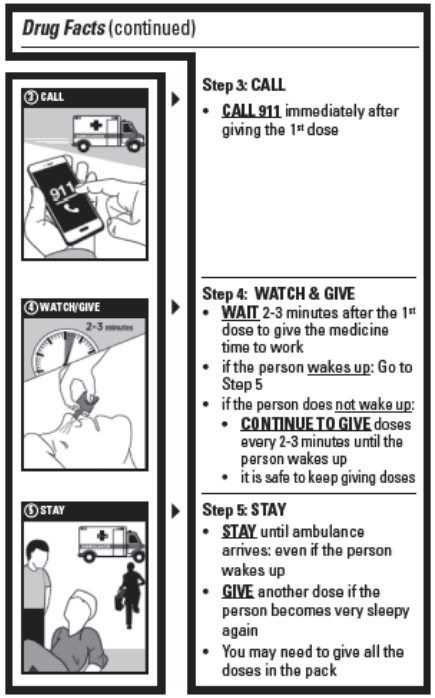
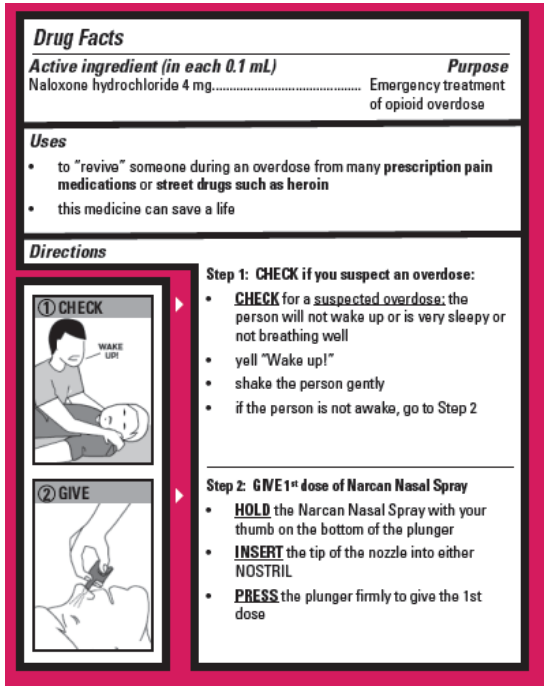
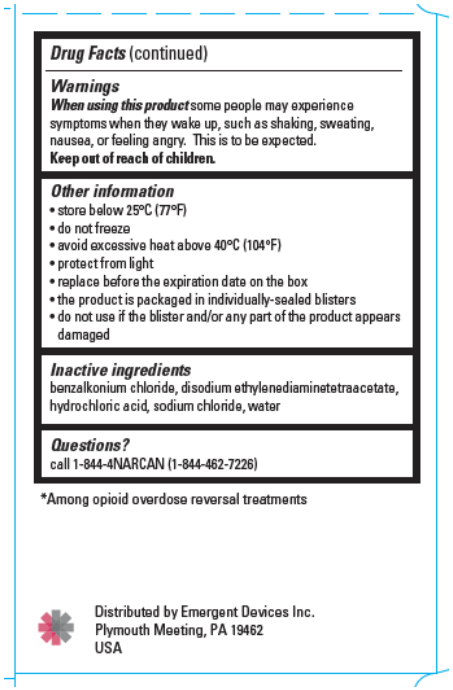
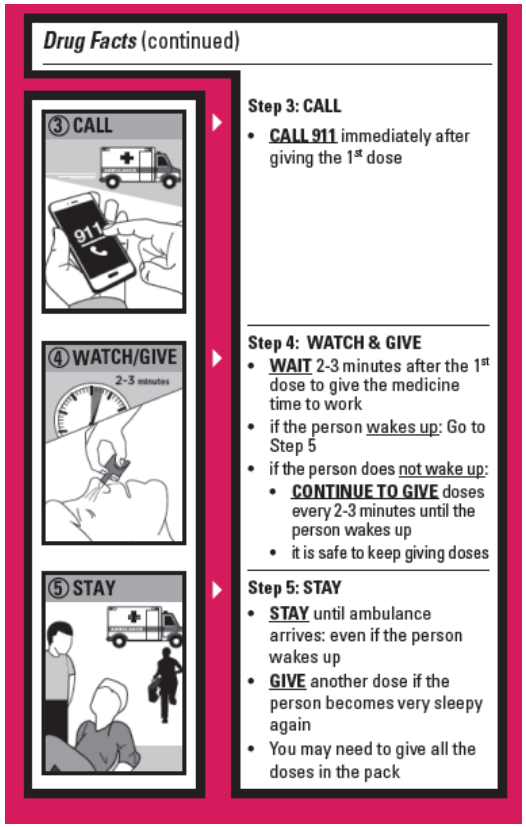
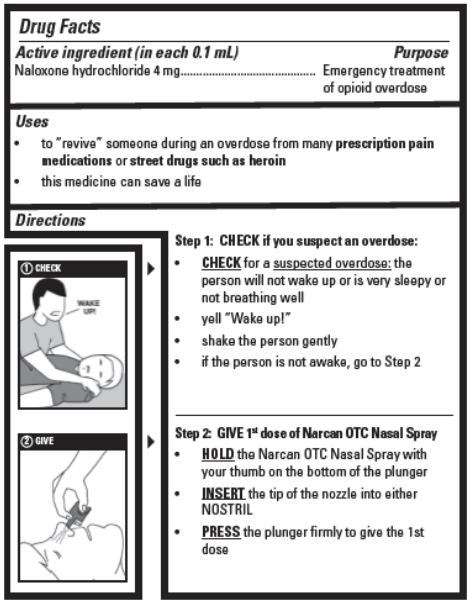


Table 5 Comparison Table of Mock OTC DFL & Carton used in Human Factors Study Compared to the Proposed Intend-to-Market (Final Proposed) Narcan DFL & Carton

HF Validation Study (Mock)	Intend-to-Market (Final Proposed)	Differences
Back Panel:  	Back Panel:  	• Previous back panel becomes left side panel • Steps 1 and 2 are moved from the right side panel to the back panel as a result of HF study • No changes in the content of labeling for Steps 1 and 2 that was tested in HF studies • Panel color updated from white to pink • Text above pictograms is updated to "gray" background and "black" text to increase readability. Additionally, the text size is increased slightly to 6.25 pt. font to increase readability • Removed "OTC" from product name in Step 2

HF Validation Study (Mock)	Intend-to-Market (Final Proposed)	Differences

Left Side Panel:
 
Drug Facts (continued)
Warnings
When using this product some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.
Keep out of reach of children.
Other information
• store below 25°C (77°F)
• do not freeze
• avoid excessive heat above 40°C (104°F)
• protect from light
• replace before the expiration date on the box
• the product is packaged in individually-sealed blisters
• do not use if the blister and/or any part of the product appears damaged
Inactive ingredients
benzalkonium chloride, disodium ethylenediaminetetraacetate, hydrochloric acid, sodium chloride, water
Questions?
call 1-844-4NARCAN (1-844-462-7226)
*Among opioid overdose reversal treatments
Distributed by Emergent Devices Inc.
Plymouth Meeting, PA 19462
USA
	Left Side Panel:
	 
	Drug Facts (continued)
	③ CALL
	Step 3: CALL
	• **CALL 911** immediately after giving the 1st dose
	④ WATCH/GIVE
	2-3 minutes
	Step 4: WATCH & GIVE
	• **WAIT** 2-3 minutes after the 1st dose to give the medicine time to work
	• if the person **wakes up**: Go to Step 5
	• if the person does **not wake up**:
	  • **CONTINUE TO GIVE** doses every 2-3 minutes until the person wakes up
	  • it is safe to keep giving doses
	⑤ STAY
	Step 5: STAY
	• **STAY** until ambulance arrives: even if the person wakes up
	• **GIVE** another dose if the person becomes very sleepy again
	• You may need to give all the doses in the pack
		• Previous left side panel content moves to right side panel
		• Steps 3, 4, and 5 are moved from back panel to the left side panel as a result of HF study
		• No changes in the content of labeling for Steps 3,4, and 5 that was tested in HF studies
		• Panel color updated from white to pink
		• Text above pictograms updated to “gray” background and “black” text to enhance readability. Additionally, the text size is increased slightly to 6.25 pt. font to increase readability

HF Validation Study (Mock)	Intend-to-Market (Final Proposed)	Differences
Right Side Panel:  **Drug Facts** **Active ingredient (in each 0.1 mL)** — **Purpose** Naloxone hydrochloride 4 mg ..... Emergency treatment of opioid overdose **Uses** • to "revive" someone during an overdose from many **prescription pain medications** or **street drugs such as heroin** • this medicine can save a life **Directions** ① CHECK ② GIVE **Step 1: CHECK if you suspect an overdose:** • **CHECK** for a suspected overdose: the person will not wake up or is very sleepy or not breathing well • yell "Wake up!" • shake the person gently • if the person is not awake, go to Step 2 **Step 2: GIVE 1st dose of Narcan OTC Nasal Spray** • **HOLD** the Narcan OTC Nasal Spray with your thumb on the bottom of the plunger • **INSERT** the tip of the nozzle into either NOSTRIL • **PRESS** the plunger firmly to give the 1st dose	Right Side Panel: **Drug Facts** (continued) **Warnings** ***When using this product*** some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected. **Keep out of reach of children.** **Other information** • store below 25°C (77°F) • do not freeze • avoid excessive heat above 40°C (104°F) • protect from light • replace before the expiration date on the box • the product is packaged in individually-sealed blisters • do not use if the blister is open or torn, or if the device appears damaged **Inactive ingredients** benzalkonium chloride, disodium ethylenediaminetetraacetate, hydrochloric acid, sodium chloride, water **Questions?** call 1-844-4NARCAN (1-844-462-7226) *Among opioid overdose reversal treatments Distributed by Emergent Devices Inc. Plymouth Meeting, PA 19462 USA NDC 69547-627-02	• Previous right side panel content (Steps 1 and 2) is moved to the back panel. Previous content on left side panel is moved to right side panel • Panel color updated from white to pink • National Drug Code moved from PDP panel to bottom corner of right side panel • The tamper evident statement under "Other information" (i.e., do not use if the blister and/or any part of the product appears damaged) was updated to "do not use if the blister is open or torn, or if the device appears damaged", to provide additional clarity for consumers on when they should not attempt to use this emergency use product. The updated statement aligns with that found in other approved nonprescription products that are provided in a blister

No changes in the content of labeling (i.e., FDA model DFL content or NARCAN-specific administration instructions) that were utilized in the HF study were made post HF validation study. The DFL content submitted in the intend-to-market (final proposed) is identical to that used in the HF validation study, with the exception of one bullet under "Other Information".

The DFL bullet "do not use if the blister and/or any part of the product appears damaged" was modified to "do not use if the blister is open or torn, or if the device appears damaged". This tamper-evident statement was updated to provide additional clarity for consumers on when they should not attempt to use this emergency use product. This updated statement more closely aligns with those found in approved nonprescription products provided in a blister.

Additionally, the blister and device labels used in the HF validation study are identical to those proposed in the intend-to-market (final proposed) with the exception of minor changes to account for compliance with current nonprescription labeling requirements (i.e., established name was updated to comply with 21 CFR 201.61(b) and the Draft FDA Guidance for Industry: Statement of Identity and Strength-Content and Format of Labeling for Human Nonprescription Drug Products (September 2022)).

3.4.1 Conclusion

The results demonstrated that the HF study was successful. The lower limit of the 95% CI exceeded the pre-defined target performance thresholds (see Table 3) for the first and second Primary Endpoints (Step 2a and Step 2b) at 90.3% (for each). While the target performance threshold of 90% was not met for the third Primary Endpoint (Step 2c) with a lower limit of the 95% CI at 86.4%, the observed proportion of correct or acceptable performance of this step was 94.4%.). Additionally, the instruction linked to this particular endpoint (i.e., "PRESS the plunger firmly…) is the same as that in current use in the prescription product. There have been no post-marketing reports to date which would indicate that these instructions are difficult to follow. There is only one post-marketing report of "device difficult to use" (refer to Table 6 and Table 7, from more than 6 years of data and approximately 44 million devices distributed).

Overall, the HF study findings support that the proposed OTC nasal naloxone DFL would be sufficient to guide correct administration of the product by a diverse group of potential user groups in an OTC setting.

4 OTC NARCAN, USER INTERFACE AND REAL WORLD POST-MARKETING DATA

4.1 Description of OTC NARCAN Nasal Spray

NARCAN delivers 4 mg of naloxone HCl in a 0.1 mL spray. The active ingredient of NARCAN is naloxone HCl. The inactive ingredients of nasal naloxone include benzalkonium chloride (a preservative common in nasal spray formulations), disodium

ethylenediaminetetraacetate (stabilizer), sodium chloride, hydrochloric acid (to adjust pH) and sterile water.

The drug product solution is administered using a nasal spray device designed to deliver 0.1 mL with each spray. The device (see Section 4.2) is a non-pressurized dispenser delivering a single spray containing a metered dose of the active ingredient, OTC nasal naloxone is not made with natural rubber latex.

OTC NARCAN is identical to Rx NARCAN (see Appendix I for the currently approved USPI) with respect to IN delivery, dosage, formulation, product active pharmaceutical ingredient and drug delivery device. In addition, OTC nasal naloxone has the same indication as the prescription product which includes both the adult and pediatric populations:

- Is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
- Intended for the immediate administration as emergency therapy in settings where opioids may be present.
- Not a substitute for emergency medical care.

NARCAN is for IN use only. The product delivers 4 mg naloxone HCl per spray. It is supplied as a single 4 mg dose of naloxone HCl in a 0.1 mL pre-filled IN spray, and in a carton containing two nasal spray devices. No additional device assembly is required.

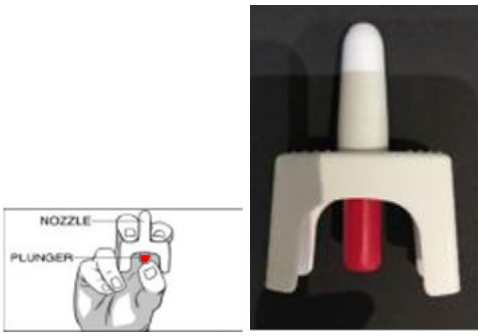
NARCAN is stored at room temperature and has a 3-year shelf-life.

Initial dosing of nasal naloxone in adults and pediatric patients is one spray delivered by IN administration, which delivers 4 mg of naloxone HCl. Repeat dosing for adults and pediatrics is the same as the current prescription nasal naloxone. Additional doses of nasal naloxone can be administered to adults and pediatrics, using a new nasal spray with each dose. If the patient does not respond or responds and then relapses into respiratory depression, additional doses of nasal naloxone may be given every 2 to 3 minutes until emergency medical assistance arrives.

4.2 Description of Device User Interface

To use the device, it is removed from the blister pack and held with the actuator top protruding between two fingers and the thumb pressing on the base of the container holder (Figure 4). When the end user presses the container holder, the holder and vial move towards the nasal actuator. This motion drives the plunger stopper against the bottom of the actuator at the actuator plunger piercing/driver region. The plunger stopper is then pierced in the reduced thickness region and liquid flows through the actuator nozzle to the tip. The orifice shape and orifice size produce a fine spray of droplets with the shape and droplet size controlled to ensure optimal nasal delivery.

Figure 4 NARCAN Nasal Spray and How Used



4.3 Real-World Post-Marketing Data Supports Layperson Usage

Effective layperson usage of NARCAN has been demonstrated since its launch. NARCAN is currently approved for use in the community use setting, and the intended use setting will not change should nasal naloxone become available as an OTC product.

From market authorization to 02OCT2022 (the current cumulative PBRER reporting period), there have been 126 reports containing 135 events of medication errors for the approximately 44 million devices distributed between the US and CA (Table 6). The reporting frequency of medication errors remains low at 0.28 per 100,000 doses distributed.

Of the cases reporting medication errors, majority consisted of reports associated with the unapproved use of IN naloxone with 52% (n= 66) associated with unintentional use for unapproved indication and 4% (n=6) reports for product use in unapproved indication. Product storage issues were reported in 8% (n=10) and product administration errors were reported in 6% (n=8) of the cases received. An assessment of the reported data presents a minimal risk for NARCAN and aligns with the analysis in the Integrated Safety Summary submitted in the NARCAN sNDA (see Appendix II, Section 1.3).

The comprehensive review of potential user error in the Emergent's safety database, FDA Adverse Event Reporting System (FAERS) Database, and the World Health Organization (WHO) International Drug Monitoring Program (VigiBase) database did not identify any unexpected findings including in the number of events associated with the route of administration. The risk of death due to opioid overdose is far greater than the risk of having naloxone administered unnecessarily, as nasal naloxone exhibits essentially no pharmacologic activity in the absence of opioids. Events of this nature are closely monitored for trends, including increases in frequency and severity during all routine stages of PV activities such as signal detection, aggregate reporting, and risk management. The overall analysis does not change the benefit-risk profile of the product.

Complaint rates for the product since its launch have remained extremely low with typically fewer than twenty complaints per year (with no trends for any particular type of complaint).

Table 6 Medication Errors Observed for NARCAN Nasal Spray–Cumulative

Preferred Term MedDRA v24.0	**Cumulative Reporting Period (N=135)**
Unintentional use for unapproved indication	66
Product storage error	10
Product administration error	8
Product use issue	7
Product use in unapproved indication	6
Expired product administered	6
Accidental exposure to product	3
Inappropriate schedule of product administration	3
Intercepted medication error	3
Product communication issue	3
Product prescribing issue	2
Product selection error	2
Incorrect route of product administration	2
Intercepted product prescribing error	2
Wrong technique in product usage process	2
Circumstance or information capable of leading to device use error	1
Circumstance or information capable of leading to medication error	1
Device difficult to use	1
Intercepted product storage error	1
Lack of administration site rotation	1
Product dispensing error	1
Product dose omission issue	1
Product label confusion	1
Product prescribing error	1
Product use complaint	1

Cumulative Reporting Period: 16FEB2016–02OCT2022 (PBRER)
Source: NARCAN Nasal Spray Periodic Benefit-Risk Evaluation Report (Approved December 2022)

All medical devices run the risk of occasional malfunction or failure. It is recognized that as a device, there is potential for failure to actuate nasal naloxone. Device failure is mitigated in the packaging configuration. The product carton contains 2 devices (doses) in the unlikely event a failure occurred on the first.

From market authorization to 02OCT2022 (the current cumulative PBRER reporting period), there have been 12 cases that reported device failures for the approximately 44 million devices distributed between the US and CA (Table 7), with a reporting frequency of 0.03 per 100,000 devices (doses) distributed. This represents a very low rate of failures. An assessment of the reported data presents a minimal risk for NARCAN and aligns with the

analysis in the Integrated Safety Summary submitted in the NARCAN sNDA (see Appendix II, Section 1.3.

Table 7 Device Failures Observed for NARCAN Nasal Spray - Cumulative

Preferred Term MedDRA v24.0	Cumulative Reporting Period (N=12)
Device issue	8
Device operational issue	1
Device breakage	1
Circumstance or information capable of leading to device use error	1
Device difficult to use	1

Cumulative Reporting Period: 16FEB2016–02OCT2022 (PBRER)

Source: NARCAN Nasal Spray Periodic Benefit-Risk Evaluation Report (Approved December 2022)

4.4 Post-Marketing Safety Surveillance

NARCAN (nasal naloxone) has over six years of safety data which remains consistent with the established product labeling.

Safety data may be received from any source including consumers, healthcare professionals, medical and product inquiries, scientific literature. All valid safety information is entered into the Emergent pharmacovigilance safety database (Argus) and reported per regulatory standards.

Post-marketing surveillance also includes the review of data from public regulatory agencies such as the FAERS and the VigiBase.

From the time of market authorization through 02OCT2022, the Emergent safety database contains 473 individual case safety reports (i.e., cases) received from any source. Of these 473 cases, 115 (24.3%) reported one or more serious adverse events (SAEs) with a fatal outcome reported in 26 (5.5%) cases. The reporting frequency of fatal cases is 0.06 in 100,000 doses distributed through October 2022.

The patient demographics of cases in the Emergent safety database are adults greater than 18 years of age; less than 2% (n=8) of cases are related to pediatric use of the product. The safety data for nasal naloxone is limited due to the under-reporting of the target population who may be afraid of the legal consequences related to reporting use of illegal substances. Medical confirmation is difficult to obtain and reported events are generally in layman's' terms. Further, the post market reports are confounded by the underlying indication for use including polysubstance abuse which frequently make adequate medical assessment difficult to achieve. Of these, MedDRA System Organ Class (SOCs) occurring in greater than 5% included:

- General disorders and administration site conditions (28.24%)
- Injury, poisoning and procedural complications (18.32%)
- Nervous system disorders (13.74%)

- Psychiatric disorders (7.63%)
- Gastrointestinal disorders (7.63%)

The summary of the comprehensive safety analysis is provided in Appendix I, Section 1.3).

There have been no new safety signals identified since market authorization. This includes findings specific to the target population or the route of administration. The patient benefit-risk ratio is well established.

NARCAN has no maximum dosage per approved USPI: therefore, it can be dosed repeatedly every 2-3 minutes until the patient responds with return of respiration or emergency medical services arrives. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists nasal naloxone exhibits essentially no pharmacologic activity.

5 OPTIMIZING OTC NARCAN ACCESSIBILITY AND EXPANDING AWARENESS

Emergent has a multi-pronged, extensive approach to support the OTC NARCAN offering, including education programs (product use/training), advancing consumer awareness (website, digital, traditional advertising), communications and advocacy. Programs will aim to accomplish these three goals:

1. Educate the public on the opioid overdose health threat
2. Drive awareness for nasal naloxone as a opioid reversal agent and the importance of readiness
3. Ease the multi-channel path to purchase

Emergent is committed to improving public health and addressing the opioid crisis. Expanding awareness and increasing accessibility to nasal naloxone continues to be at the forefront of Emergent's work with patients, families, caregivers, healthcare providers, first responders, pharmacists, Federal and state governments, and insurers across the US.

Over-the-counter (OTC) status, if approved, is just one mechanism that will help to achieve more equitable access to naloxone. OTC designation does not mitigate the need for healthcare provider dialogue around the risk of an opioid overdose, nor does it remove the need for policies and solutions that increase education and awareness of these medications and the risk of accidental opioid overdose among at-risk communities. Emergent believes addressing the opioid crisis is a collaborative effort, and partnership with stakeholders is critical to supporting those who need it to obtain naloxone. This includes, but is not limited to:

- Education, e.g., product use/administration training

- Federal, state, and, local government programs, Consumer awareness tools, (e.g., website, digital and traditional advertising)
- Communications/public relations announcements, advocacy and third-party engagement, and collaboration with other external groups

Emergent is committed to partnership and collaboration with stakeholders, including the Federal and state governments to increase access to and awareness of naloxone.

6 BENEFIT-RISK ASSESSMENT OF OTC NARCAN

The current opioid epidemic is one of the most critical public health issues in the US. The Centers for Disease Control and Prevention (CDC) has reported that nearly one million people have died from a drug overdose in the US since the Agency began collecting such data in 1999, and that this number is primarily driven by opioid overdoses (CDC, 2022). The opioid overdose waves over the past three decades have resulted from different etiologies. The first wave was associated with prescription opioid overdose deaths and started in 1999, wave two was associated with the rise in heroin and overdose deaths from 1999 to 2013. The third wave occurred with a rise in synthetic opioid overdose deaths started in 2013. Unfortunately, the fourth wave continues to escalate with increasing number of opioid overdose deaths as a confluence of factors including the CDC 2016 guidelines, the COVID pandemic, increased availability of illicit synthetic opioids, and the reduction of access to interventional techniques, which leads patients to seek remedies on their own (Manchikanti, 2022). Ciccarone first described the fourth wave of drug overdose deaths involving methamphetamine and cocaine, with the increasing use of illicit fentanyl as the major drivers of overdose deaths (Ciccarone, 2021). There has been a decrease in opioid prescriptions (43% decrease in 2020 compared to 2010) yet drug overdose deaths have not decreased, but increased 140% from 2010 to 2020. The following are US Opioid Epidemic numbers 2020 compared to 2019 (Manchikanti, 2022,):

- 75,673 drug overdose deaths involved an opioid, increase of 34.9%
- 23,837 deaths involving psychostimulants (primarily methamphetamine), increase of 47.4%
- 13,165 deaths involving heroin, decrease of 6.1%
- 16,416 deaths involving natural and semi-synthetic opioids (Rx), increase of 16.1%
- Average 207 opioids deaths/day (Rx opioids 44.9 deaths/day)

6.1 Medical Need for OTC Nasal Naloxone

Naloxone HCl was initially approved by the FDA in 1971 (Narcan, NDA 016636), and has been used for more than 50 years to treat opioid-induced respiratory depression, with robust safety data available (NDA 016636). Naloxone is the standard of care for treatment of opioid induced respiratory depression reversing a potentially fatal opioid overdose event. It was traditionally utilized by medically trained personnel, such as clinicians and paramedics

(Seal, 2005). However, 75% of opioid overdose deaths happened outside medical facilities, and most frequently opioid overdoses occur in the decedent's home (53%) (CDC Wonder Database, 2018). This facet of the opioid crisis led to the development and subsequent FDA approval of naloxone in the community setting (i.e., THN).

Despite the availability of numerous Rx take home naloxone products, there continues to be a need to further increase access to naloxone. Expanding access to naloxone is a critical component of the public policy response to the opioid overdose epidemic. All 50 states have implemented law(s) to expand access to naloxone, and to limit liability of those who provide care in an emergency. Standing orders, collaborative practice agreements, and local protocols have provided naloxone pharmacy access to patients and their caregivers (families) without requiring an individual prescription. Additionally, Federal and state agencies have contributed to increasing naloxone supply and a growing list of organizations are now equipped with naloxone, including, law enforcement, firefighters, EMS, and harm reduction groups.

"Expanded access and co-prescribing are significant tools to enhance availability, but more is needed - not everyone can/wants to obtain naloxone by seeing a healthcare professional," per CDER (Center for Drug Evaluation and Research) webinar: FDA Drug topics: An Overview of Naloxone and FDA's efforts to expand access, September 29, 2020). Broader access to nasal naloxone by switching from prescription to OTC is critical to help respond to the current opioid epidemic and prevent avoidable deaths.

Evoy et al published on Opioid Related Overdose (ORO) and discussed the need to have naloxone available in a timely fashion in order to prevent long term morbidity and mortality. They suggested increased in access of naloxone to people at risk is a crucial step in reducing ORO. (Evoy et al., 2021).

Recent data from the CDC show that bystanders were present at 45% of fatal opioid overdoses, naloxone was administered in only approximately 4% of cases (Mattson et al., 2018). Eliminating this gap represents a critical opportunity to reduce opioid-related deaths (Davis, 2020).

6.2 Overdose Education and Naloxone Distribution (OEND) Reduce Overdose Deaths

Since 1996, community-based programs and state public health programs have offered OEND for bystander administration to people who use opioids, particularly heroin, outside the medical setting (Mueller et al., 2015). Overdose education and naloxone distribution have been an essential and necessary approach to address this epidemic and reduce overdose deaths.

Naloxone administration must occur in a timely manner (NARCAN USPI, see Appendix I). This expansion requires outreach, education, and distribution outside traditional avenues, including in the lay community, harm reduction organizations, and criminal justice settings, among others. Irvine et al reported in a recent article modeling data that suggests that based on the current distribution of naloxone to achieve a target of naloxone use in 80% of witnessed overdoses, the need varied from no additional kits (estimated as sufficient) to 1270

kits needed per 100,000 population across the 12 modeled states annually. Authors conclude that the extent of naloxone distribution, especially through community-based programs and pharmacy-initiated access points, warrants substantial expansion in nearly every US state (Irvine, 2022).

Wenger et al states, OEND programs, essentially train laypeople—people who use drugs, family members, peers by providing access to naloxone and training for its administration (Wenger LD, 2022). A strong body of research has shown that OEND can be highly effective and cost-effective at preventing opioid overdose mortality (Wenger LD, 2022), and that training people who are at risk for overdose and their peers is a feasible and effective way to prevent mortality from overdose (Mueller, 2015, Walley 2013, Strang, 2008). Studies have shown that people who are at risk for overdose, and other bystanders, are willing and able to be trained to prevent overdoses and administer naloxone. For this reason, Emergent is committed to providing education and awareness for its OTC nasal naloxone, as outlined in Section 5.

6.3 Special Considerations: Abuse/Misuse and Drug Risk Behaviour

The potential for abuse or misuse is an important consideration for all medications used in OTC conditions, whether unintentional or driven by therapeutic intent. In the specific case of OTC nasal naloxone, there have been concerns on whether the expansion of naloxone distribution would lead to issues of altered drug use frequency, quantity or severity.

Through Emergent's robust pharmacovigilance practices, the misuse potential of nasal naloxone has been assessed as minimal. Per Section 4.3, post-marketing data show minimal misuse by subjects.

Limited research has also demonstrated that misuse potential is low. Jones et al, published data on a study that assessed whether participation in naloxone/overdose training altered drug use frequency, quantity or severity among heroin users in and out of treatment. This publication found no evidence of compensatory drug use following naloxone/ overdose training among two groups of heroin users. These findings support the acceptance and expansion of naloxone distribution to at-risk populations and may assist in allaying concerns about the potential for unintended negative consequences on drug use. (Jones Addict Behav. 2017 August ; 71: 104–106. doi:10.1016/j.addbeh.2017.03.008.)

Lai et al (2020) also published from a pilot study on drug users perspectives of naloxone. This study evaluated naloxone distribution programs and the effects of increasing naloxone availability on the behavior of people who use drugs. It evaluated drug use patterns and perceptions to naloxone. Participants were accepting of, and knowledgeable about naloxone, and were willing to administer naloxone to save a life. They tended to use opioids more cautiously when naloxone was present due to fears of experiencing precipitated withdrawal. This study provides evidence that further supports naloxone access (Lai et al., 2020).

Emergent takes these concerns seriously and will continue to monitor safety data of OTC NARCAN, collecting data received from any source including consumers, healthcare professionals, product inquiries, complaints, and scientific literature, and suggesting corrective action, as needed. Safety signals are reviewed by the Emergent PV department in accordance with Emergent procedures and FDA pharmacovigilance reporting requirements.

6.4 OTC NARCAN has a Favorable Benefit-Risk Profile

NARCAN has a proven benefit-risk profile with a wealth of post-marketing experience. The safety and efficacy findings for nasal naloxone in community-use settings, support the clinical benefit of the product. NARCAN can help save lives.

- NARCAN has a relatively low risk profile,
- It is easy to use in emergency situations with minimal training, is light to carry, with no needle-stick injury risk
- Nasal naloxone provides a consistent concentration of naloxone in each dose.

Giglio RE, et al., concluded that opioid overdose education and bystander naloxone administration are safe and effective in a community-based approach. Furthermore, there are increased odds of recovery and increased knowledge of opioid overdose recognition and management. (Giglio et al., 2015).

Decades of empirical and qualitative evidence demonstrate that laypeople can recognize opioid overdose with little or no training, and that those individuals can and will use naloxone appropriately (Bennett et al., 2018; Doe-Simkins et al., 2014). Naloxone is a safe medication, with no contraindications other than hypersensitivity to the medication. It has no potential for misuse and produces no negative effects if administered to a person incorrectly identified as experiencing an overdose (Chamberlain and Klein, 1994).

Naloxone HCl, the active pharmaceutical ingredient, is not a controlled substance and has no known abuse potential.

In the presence of physical dependence on opioids, naloxone will produce withdrawal symptoms, which may appear within minutes of naloxone administration and will subside in about 2 hours (refer to USPI “Precipitation of Severe Opioid Withdrawal (Appendix I, Section 5.3).

Use of nasal naloxone continues to have a favorable benefit-risk profile for the emergency treatment of known or suspected opioid overdose. The potential life-saving benefits of administering nasal naloxone outweigh the risks of failure to reverse overdose when used with other appropriate measures (e.g., calling 911).

7 SUMMARY AND CONCLUSIONS

- Opioid overdose and opioid induced respiratory depression are significant life-threatening conditions and are a critical public health issue in the US

- Nasal naloxone, through its ability to reverse opioid induced respiratory depression in the emergency setting, has been shown to save lives
- Broadening access to nasal naloxone by switching from prescription to OTC has been deemed by FDA and other stakeholders to be critical to help respond to the current opioid epidemic – the majority of opioid deaths occur in the community setting. The key to its effectiveness is in its availability and rapid deployment by a lay person in the setting where it is needed
- NARCAN meets the regulatory requirements for OTC status based on the evidence, suggesting that it can be safely and effectively used without the involvement of a healthcare professional and that such use does not result in any untoward downstream consequences
- Emergent conducted a HF study to evaluate the effectiveness of the proposed NARCAN-specific DFL, which was a reproduction of the FDA-developed model intranasal naloxone DFL and with minimal additions to include product-specific information and directions. To confirm its ability to guide appropriate use, testing included users from various backgrounds, including low literacy level and adolescents. Testing confirmed the product can be used safely and effectively, in the OTC setting, including low literacy and adolescent subjects
- NARCAN has over six years of post-marketing safety data, with approximately 44 million devices (doses) distributed in the US and CA as per current cumulative PBRER reporting period (to 02 OCT 2022)
- NARCAN has a relatively low risk profile, is easy to use in emergency situations with minimal to no formal training, has no needle-stick injury risk, and provides a consistent concentration of naloxone in each dose. There is no risk of overdose making it appropriate for use by layperson by-standers
- Cases of medication error and other product user errors for NARCAN are minimal (reporting frequency 0.28 per 100,000 doses). Device failure is also reported infrequently (reporting frequency 0.03 per 100,000 doses)
- There is no evidence that the broader availability of nasal naloxone would have consequences with respect to enhancing more risky behavior with respect to drug use. Experience with use in the community setting has not demonstrated any additional risks
- Emergent has a multi-pronged, extensive approach to support the OTC NARCAN offering, including education programs (product use/training), advancing consumer awareness (website, digital, traditional advertising), communications and advocacy
- Emergent will continue to monitor safety data of OTC NARCAN, collecting data received from any source including consumers, healthcare professionals, product inquiries, complaints, and scientific literature
- The favorable benefit-risk profile of NARCAN will remain unchanged in the switch to OTC. Expanding access to OTC NARCAN beyond the current distribution

methods, will help remove barriers to access and allow anyone to be administered naloxone rapidly, by a layperson, providing timely access to a potentially life-saving medicine until emergency services arrive.

8 REFERENCES

FDA. Drugs@ FDA Database. NDA 016636. April 3, 1971. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016636

FDA. Center for Drug Evaluation and Research. NDA 208411. November 18, 2015. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000SumR.pdf

Centers for Disease Control and Prevention (CDC)/ National Center for Injury Prevention and Control. Injuries and Violence Are Leading Causes of Death. February 28, 2022. Accessed January 10, 2023. https://www.cdc.gov/injury/wisqars/animated-leading-causes.html#:~:text=The%20leading%20causes%20of%20death,unintentional%20drowning%2C%20and%20unintentional%20falls.

Centers for Disease Control and Prevention (CDC)/ National Center for Injury Prevention and Control. Death Rate Maps & Graphs. June 2, 2022. Accessed January 10, 2023. https://www.cdc.gov/drugoverdose/deaths/index.html

Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics. Drug Overdose Deaths in the U.S. Top 100,000 Annually. November 17, 2021. Accessed December 13, 2022. https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm

Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics. U.S. Overdose Deaths In 2021 Increased Half as Much as in 2020 – But Are Still Up 15%. May 11, 2022. Accessed January 10, 2023. https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm

Meyerson BE, Agley JD, Davis A, Jayawardene W, Hoss A, Shannon DJ, et al. Predicting pharmacy naloxone stocking and dispensing following a statewide standing order, Indiana 2016. Drug Alcohol Depend. 2018;188:187-92.

Stone RH, Hur S, Young HN. Assessment of naloxone availability in Georgia community pharmacies. J Am Pharm Assoc (2003). 2020;60(2):357-61.

Graves RL, Andreyeva E, Perrone J, Shofer FS, Merchant RM, Meisel ZF. Naloxone Availability and Pharmacy Staff Knowledge of Standing Order for Naloxone in Pennsylvania Pharmacies. J Addict Med. 2019;13(4):272-8.

Sisson ML, McMahan KB, Chichester KR, Galbraith JW, Cropsey KL. Attitudes and availability: A comparison of naloxone dispensing across chain and independent pharmacies in rural and urban areas in Alabama. Int J Drug Policy. 2019;74:229-35.

Thompson EL, Rao PSS, Hayes C, Purtill C. Dispensing Naloxone Without a Prescription: Survey Evaluation of Ohio Pharmacists. J Pharm Pract. 2019;32(4):412-21.

Evoy KE, Hill LG, Davis CS. Considering the Potential Benefits of Over-the-Counter Naloxone. Integr Pharm Res Pract. 2021;10:13-21.

Office of the Federal Register, National Archives and Records Administration. 2022, November 15. 87 FR 68702

(ref.https://www.federalregister.gov/documents/2022/11/16/2022-24874/safety-and-effectiveness-of-certain-naloxone-hydrochloride-drug-products-for-nonprescription-use)

U.S. Food & Drug Administration (FDA). Comprehension for OTC Naloxone (CONFER) Pivotal Label Comprehension Study - FDA Review of Task 3 Study Report. January 17, 2019. Accessed January 10, 2023. https://www.fda.gov/media/119745/download

Krieter P, Chiang N, Gyaw S, et al. Pharmacokinetic Properties and Human Use Characteristics of an FDA-Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose. J Clin Pharmacol. 2016;56(10):1243-1253.

Wheeler E, Jones TS, Gilbert MK, Davidson PJ; Centers for Disease Control and Prevention (CDC). Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014. MMWR Morb Mortal Wkly Rep. 2015;64(23):631-635.

Doe-Simkins M, Quinn E, Xuan Z, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. BMC Public Health. 2014;14:297.

Rowe C, Santos GM, Vittinghoff E, Wheeler E, Davidson P, Coffin PO. Predictors of participant engagement and naloxone utilization in a community-based naloxone distribution program. Addiction. 2015;110(8):1301-1310.

Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ. 2013;346:f174

FDA Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products (August 2010).

Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (February 2016).

Murphy, Peggy W.; Davis, Terry C.; Long, Sandra W.; Jackson, Robert H.; Decker, Barbara C. Rapid Estimate of Adult Literacy in Medicine (REALM): a quick reading test for patients. Journal of Reading. 1993 Oct; 37(2):124-30.

Davis TC, Wolf MS, Arnold CL, Byrd RS, Long SW, Springer T, et al. Development and validation of the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen): A tool to screen adolescents for below-grade reading in health care settings. Pediatrics. 2006 118(6): e1707-1714.

Jones CM, Einstein EB, Compton WM. Changes in synthetic opioid involvement in drug overdose deaths in the United States, 2010-2016. Jama. 2018;319(17):1819-21.

O'Donnell JK, Halpin J, Mattson CL, Goldberger BA, Gladden RM. Deaths involving fentanyl, fentanyl analogs, and U-47700—10 states, July–December 2016. MMWR Morb Mortal Wkly Rep. 2017;66(43):1197.

Draft FDA Guidance for Industry: Statement of Identity and Strength-Content and Format of Labeling for Human Nonprescription Drug Products (September 2022).

Manchikanti L, Singh VM, Staats PS, et al. Fourth Wave of Opioid (Illicit Drug) Overdose Deaths and Diminishing Access to Prescription Opioids and Interventional Techniques: Cause and Effect. *Pain Physician*. 2022;25(2):97-124.

Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. *Curr Opin Psychiatry*. 2021;34(4):344-350.

Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December 2018. Data are from the Multiple Cause of Death Files, 1999-2017, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. http://wonder.cdc.gov/mcd-icd10.html Accessed March 20, 2019.

Seal KH, Thawley R, Gee L, et al. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study. *J Urban Health*. 2005;82(2):303-311.

Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. Multiple Cause of Death
1999-2017 on CDC WONDER Online Database, released December 2018. Data are from the Multiple Cause of Death Files, 1999-2017, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics
Cooperative Program. http://wonder.cdc.gov/mcd-icd10.html Accessed March 20, 2019.

Mattson CL, O'Donnell J, Kariisa M, Seth P, Scholl L, Gladden RM. Opportunities to Prevent Overdose Deaths Involving Prescription and Illicit Opioids, 11 States, July 2016-June 2017. MMWR Morb Mortal Wkly Rep. 2018;67(34):945-951.

Mueller SR, Walley AY, Calcaterra SL, Glanz JM, Binswanger IA. A Review of Opioid Overdose Prevention and Naloxone Prescribing: Implications for Translating Community Programming Into Clinical Practice. *Subst Abus*. 2015;36(2):240-253.

Irvine MA, Oller D, Boggis J, et al. Estimating naloxone need in the USA across fentanyl, heroin, and prescription opioid epidemics: a modelling study. *Lancet Public Health*. 2022;7(3):e210-e218.

Wenger, L.D., Doe-Simkins, M., Wheeler, E. *et al.* Best practices for community-based overdose education and naloxone distribution programs: results from using the Delphi approach. *Harm Reduct J* **19**, 55 (2022).

Strang J, Manning V, Mayet S, et al. Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses. *Addiction*. 2008;103(10):1648-1657.

Jones Addict Behav. 2017 August ; 71: 104–106. doi:10.1016/j.addbeh.2017.03.008.

Lai JT, Goldfine CE, Chapman BP, et al. Nobody Wants to Be Narcan'd: A Pilot Qualitative Analysis of Drug Users' Perspectives on Naloxone. West J Emerg Med. 2021;22(2):339-345.

Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. Inj Epidemiol. 2015;2(1):10.

Bennett AS, Bell A, Doe-Simkins M, Elliott L, Pouget E, Davis C. From Peers to Lay Bystanders: Findings from a Decade of Naloxone Distribution in Pittsburgh, PA. J Psychoactive Drugs. 2018;50(3):240-246.

FDA. NARCAN Nasal Spray Prescribing Information 2020[Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=724df050-5332-4d0a-9a5f-17bf08a547e1.

Chamberlain JM, Klein BL. A comprehensive review of naloxone for the emergency physician. Am J Emerg Med. 1994;12(6):650-660.

APPENDIX I CURRENT PRESCRIPTION NARCAN LABELING

NARCAN- naloxone hydrochloride spray
Emergent Devices Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NARCAN® NASAL SPRAY safely and effectively. See full prescribing information for NARCAN® NASAL SPRAY.
NARCAN® (naloxone hydrochloride) nasal spray
Initial U.S. Approval: 1971

INDICATIONS AND USAGE

NARCAN Nasal Spray is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. (1)
NARCAN Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present. (1)
NARCAN Nasal Spray is not a substitute for emergency medical care. (1)

DOSAGE AND ADMINISTRATION

- NARCAN Nasal Spray is for intranasal use only. (2.1)
- Seek emergency medical care immediately after use. (2.1)
- Administration of a single spray of NARCAN Nasal Spray intranasally into one nostril. (2.2)
- Administer additional doses of NARCAN Nasal Spray, using a new nasal spray with each dose, if the patient does not respond or responds and then relapses into respiratory depression, additional doses of NARCAN Nasal Spray may be given every 2 to 3 minutes until emergency medical assistance arrives. (2.2)
- Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance. (2.2)

DOSAGE FORMS AND STRENGTHS

Nasal spray: 2 mg and 4 mg of naloxone hydrochloride in 0.1 mL. (3)

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 pre-existing 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, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, rhinalgia, and xeroderma. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Emergent Devices Inc. at 1-844-4NARCAN (1-844-462-7226) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
2.2 Dosing in Adults and Pediatric Patients
2.3 Dosing Modifications due to Partial Agonists or Mixed Agonist/Antagonists
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Risk of Recurrent Respiratory and Central Nervous System Depression
5.2 Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists
5.3 Precipitation of Severe Opioid Withdrawal
6 ADVERSE REACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NARCAN Nasal Spray is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

NARCAN Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present.

NARCAN Nasal Spray is not a substitute for emergency medical care.

Limitations of Use:

Restrict prescription of NARCAN Nasal Spray 2 mg to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

NARCAN Nasal Spray is for intranasal use only.

No additional device assembly is required.

Because treatment of suspected opioid overdose must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about the presence of NARCAN Nasal Spray and the *Instructions for Use.*

Instruct the patient or caregiver to read the *Instructions for Use* at the time they receive a prescription for NARCAN Nasal Spray. Emphasize the following instructions to the patient or caregiver:

- Administer NARCAN Nasal Spray as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death. Since the duration of action of most opioids exceeds that of naloxone hydrochloride and the suspected opioid overdose may occur outside of supervised medical settings, seek immediate emergency medical assistance, keep the patient under continued surveillance until emergency personnel arrive, and administer repeated doses of NARCAN Nasal Spray, as necessary. Always seek emergency medical assistance in the event of a suspected, potentially life-threatening opioid emergency after administration of the first dose of NARCAN Nasal Spray.
- Additional doses of NARCAN Nasal Spray may be required until emergency medical assistance becomes available.
- Do not attempt to reuse NARCAN Nasal Spray. Each NARCAN Nasal Spray contains a single dose of naloxone and cannot be reused.
- Re-administer NARCAN Nasal Spray, using a new nasal spray, every 2 to 3 minutes if the patient does not respond or responds and then relapses into respiratory depression.
- Administer NARCAN Nasal Spray in alternate nostrils with each dose.
- Administer NARCAN Nasal Spray according to the printed instructions on the device label and the *Instructions for Use*.
- Place the patient in the supine position. Prior to administration, be sure the device nozzle is inserted in either nostril of the patient, and provide support to the back of the neck to allow the head to tilt back. **Do not prime or test the device prior to administration.**
- To administer the dose press firmly on the device plunger.
- Remove the device nozzle from the nostril after use.
- Turn patient on their side as shown in the *Instructions for Use* and call for emergency medical assistance immediately after administration of the first dose of NARCAN Nasal Spray.

2.2 Dosing in Adults and Pediatric Patients

Initial Dosing

The recommended initial dose of NARCAN Nasal Spray in adults and pediatric patients is one spray delivered by intranasal administration into one nostril.

Repeat Dosing

Seek emergency medical assistance as soon as possible after administering the first dose of NARCAN Nasal Spray.

The requirement for repeat doses of NARCAN Nasal Spray depends upon the amount, type, and route of administration of the opioid being antagonized.

Administer NARCAN Nasal Spray in alternate nostrils with each dose.

If the patient responds to NARCAN Nasal Spray and relapses back into respiratory depression before emergency assistance arrives, administer an additional dose of NARCAN Nasal Spray using a new NARCAN Nasal Spray and continue surveillance of the patient.

If the desired response is not obtained after 2 or 3 minutes, administer an additional dose of NARCAN Nasal Spray using a new NARCAN Nasal Spray. If there is still no response and additional doses are available, administer additional doses of NARCAN Nasal Spray every 2 to 3 minutes using a new NARCAN Nasal Spray with each dose until emergency medical assistance arrives.

Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

2.3 Dosing Modifications due to Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and require higher doses of naloxone hydrochloride or repeated administration of NARCAN Nasal Spray using a new nasal spray *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

NARCAN Nasal Spray is supplied as a single-dose intranasal spray containing 2 mg or 4 mg of naloxone hydrochloride in 0.1 mL.

4 CONTRAINDICATIONS

NARCAN Nasal Spray is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Recurrent Respiratory and Central Nervous System Depression

The duration of action of most opioids may exceed that of NARCAN Nasal Spray resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Therefore, it is necessary to seek emergency medical

assistance immediately after administration of the first dose of NARCAN Nasal Spray and to keep the patient under continued surveillance. Administer additional doses of NARCAN Nasal Spray if the patient is not adequately responding or responds and then relapses back into respiratory depression, as necessary *[see Dosage and Administration (2.2)]*. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

5.2 Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses of naloxone hydrochloride may be required to antagonize buprenorphine because the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor *[see Dosage and Administration (2.3)]*. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

5.3 Precipitation of Severe Opioid Withdrawal

The use of NARCAN Nasal Spray in patients who are opioid-dependent may precipitate opioid withdrawal characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes. Monitor the patient for the development of the signs and symptoms of opioid withdrawal.

There are limited data to inform if the 2 mg dose of NARCAN Nasal Spray will avoid precipitation of severe opioid withdrawal in the setting of opioid dependence. However, the 2 mg dose may not provide an adequate and timely reversal in persons who may be exposed to an overdose of a potent or very high dose of opioids.

Abrupt postoperative reversal of opioid depression after using naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, monitor patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

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. In these settings, consider use of an alternative, naloxone-containing product that can be titrated to effect and, where applicable, dosed according to weight. *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Precipitation of Severe Opioid Withdrawal *[see Warnings and Precautions (5.3)]*

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse reactions were observed in a NARCAN Nasal Spray clinical study.

In a pharmacokinetic study of 30 healthy adult volunteers exposed to one spray of NARCAN Nasal Spray in one nostril or two sprays of NARCAN Nasal Spray, one in each nostril, the most common adverse reactions were: increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, rhinalgia, and xeroderma.

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.

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated an acute withdrawal syndrome. Signs and symptoms have included: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In some patients, there may be aggressive behavior upon abrupt reversal of an opioid overdose. In the neonate, opioid withdrawal signs and symptoms also included convulsions, excessive crying, and hyperactive reflexes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on naloxone use in pregnant women are not sufficient to inform a drug-associated risk. However, there are clinical considerations *[see Clinical Considerations]*. In animal reproduction studies, no embryotoxic or teratogenic effects were observed in mice and rats treated with naloxone hydrochloride during the period of organogenesis at doses equivalent to 6-times and 12-times, respectively, a human dose

of 8 mg/day (two NARCAN Nasal Sprays) based on body surface area comparison *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Naloxone hydrochloride crosses the placenta, and may precipitate withdrawal in the fetus, as well as in the opioid-dependent mother *[see Warnings and Precautions (5.3)]*. The fetus should be evaluated for signs of distress after NARCAN Nasal Spray is used. Careful monitoring is needed until the fetus and mother are stabilized.

Data

Animal Data

Naloxone hydrochloride was administered during organogenesis to mice and rats at subcutaneous doses up to 10 mg/kg/day (equivalent to 6-times and 12-times, respectively, a human dose of 8 mg (two NARCAN Nasal Sprays)) (based on body surface area comparison). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.

Pregnant female rats were administered 2 or 10 mg/kg naloxone subcutaneously from Gestation Day 15 to Postnatal day 21. There were no adverse effects on the offspring (up to 12-times a human dose of 8 mg/day (two NARCAN Nasal Sprays) based on body surface area comparison).

8.2 Lactation

Risk Summary

There is no information regarding the presence of naloxone in human milk, or the effects of naloxone on the breastfed infant or on milk production. Studies in nursing mothers have shown that naloxone does not affect prolactin or oxytocin hormone levels. Naloxone is minimally orally bioavailable.

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.

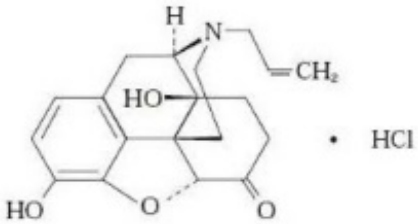
8.5 Geriatric Use

Geriatric patients have a greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Therefore, the systemic exposure of naloxone hydrochloride can be higher in these patients.

Clinical studies of naloxone hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

NARCAN (naloxone hydrochloride) Nasal Spray is a pre-filled, single dose intranasal spray. Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:



$C_{19}H_{21}NO_4$• HCl
M.W. 363.84

Naloxone hydrochloride, an opioid antagonist, occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Each NARCAN Nasal Spray contains a 2 mg or 4 mg single dose of naloxone hydrochloride (equivalent to 1.8 mg or 3.6 mg of naloxone) in a 0.1 mL (100 microliter) aqueous solution.

Inactive ingredients include benzalkonium chloride (preservative), disodium ethylenediaminetetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH,

and purified water. The pH range is 3.5 to 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naloxone hydrochloride is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites.

Naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension. It can also reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

12.2 Pharmacodynamics

When naloxone hydrochloride is administered intravenously, the onset of action is generally apparent within two minutes. The time to onset of action is shorter for intravenous compared to subcutaneous or intramuscular routes of administration. The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride.

12.3 Pharmacokinetics

In a pharmacokinetic study in 30 healthy adult subjects, the relative bioavailability (BA) of one nasal spray in one nostril, consisting of a 2 mg total dose (0.1 mL of 20 mg/mL naloxone hydrochloride solution) and a 4 mg total dose (0.1 mL of 40 mg/mL naloxone hydrochloride solution), and two nasal sprays administered as one nasal spray in each nostril, consisting of a 4 mg total dose (0.1 mL of 20 mg/mL naloxone hydrochloride solution in each nostril) and an 8 mg total dose (0.1 mL of 40 mg/mL naloxone hydrochloride solution in each nostril), were compared to a single dose of 0.4 mg naloxone hydrochloride intramuscular injection. For intranasal administration, the subjects were instructed not to breathe through the nose during administration of the nasal spray, and remained fully supine for approximately one hour post-dose. For intramuscular administration, naloxone was administered as a single injection in the gluteus maximus muscle. The pharmacokinetic parameters obtained in the study are shown in Table 1.

Table 1 Mean Pharmacokinetic Parameters (CV%) for Naloxone Following NARCAN (Naloxone HCl) Nasal Spray and Intramuscular Injection of Naloxone HCl to Healthy Subjects

Parameter	2 mg – One Nasal Spray in one nostril 20 mg/ml (N=29)	4 mg – Two Nasal Sprays, one in each nostril 20 mg/ml (N=29)	4 mg – One Nasal Spray in one nostril 40 mg/ml (N=29)	8 mg –Two Nasal Sprays, one in each nostril 40 mg/ml (N=29)	0.4 mg Intramuscular Injection (N=29)
t_{max} (h)*	0.33 (0.25, 1.00)	0.33 (0.17, 0.57)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)

C_{max} (ng/mL)	2.91 (35)	6.30 (34)	4.83 (43)	9.70 (36)	0.88 (31)
AUCt (hr.ng/mL)	4.60 (27)	9.64 (24)	7.87 (37)	15.3 (23)	1.75 (23)
AUC_{0-inf} (h*ng/mL)	4.66 (27)	9.74 (24)	7.95 (37)	15.5 (23)	1.79 (23)
t½ (h)	1.85 (33)	2.19 (33)	2.08 (30)	2.10 (32)	1.24 (26)
Dose normalized Relative BA (%) vs. IM	51.7 (22)	54.0 (23)	44.2 (31)†	43.1 (24)	100

* t_{max} reported as median (minimum, maximum)
† N=28 for Relative BA.

Figure 1 Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection

(a)

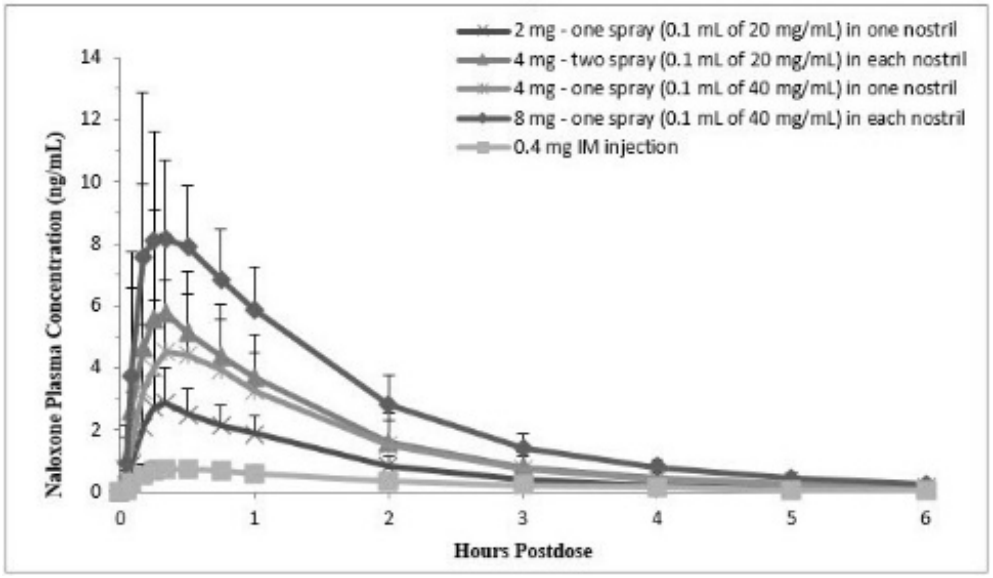


Figure 1 Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection

(b)

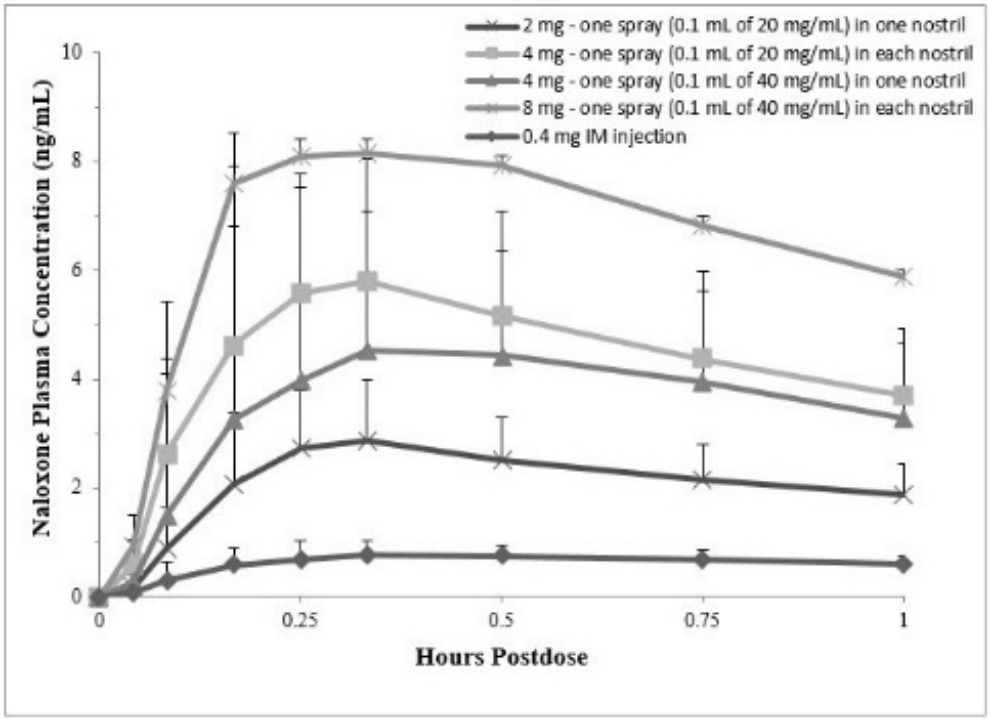


Figure 1 Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection

The median naloxone t_{max} after intranasal administration of NARCAN Nasal Spray (one nasal spray in one nostril (2 mg or 4 mg) or two nasal sprays as one spray in each nostril (4 mg or 8 mg) was not significantly different compared to the 0.4 mg dose of naloxone hydrochloride intramuscular injection (Table 1).

The dose normalized relative bioavailability of one dose (2 mg or 4 mg) or two doses (4 mg or 8 mg) of NARCAN Nasal Spray as compared to the 0.4 mg dose of naloxone hydrochloride administered by intramuscular injection was 52%, 44%, 54%, and 43%, respectively.

Distribution

Following parenteral administration, naloxone is distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent, but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

Elimination

Following a single intranasal administration of NARCAN Nasal Spray (2 mg or 4 mg dose of naloxone hydrochloride), the mean plasma half-life of naloxone in healthy adults was approximately 1.85 (33% CV) hours and 2.08 (30% CV) hours; respectively, which was longer than that observed after administrations of a 0.4 mg naloxone hydrochloride intramuscular injection, where the half-life was 1.24 hours (26% CV). In a neonatal study of naloxone hydrochloride injection, the mean (± SD) plasma half-life was observed to be 3.1 (± 0.5) hours.

Metabolism

Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation, with naloxone-3-glucoronide as the major metabolite.

Excretion

After an oral or intravenous dose, about 25-40% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed.

Mutagenesis

Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.

Impairment of Fertility

Male rats were treated with 2 or 10 mg/kg naloxone for 60 days prior to mating. Female rats treated for 14-days prior to mating and throughout gestation with the same doses of naloxone (up to 12-times a human dose of 8 mg/day (two NARCAN Nasal Sprays) based on body surface area comparison). There was no adverse effect on fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NARCAN Nasal Spray 2 mg is supplied as a carton containing four (4) blister packages (NDC 69547-212-04) each with a single spray device and as a carton containing twenty-four (24) blister packages (NDC 69547-212-24) each with a single spray device.

NARCAN Nasal Spray 4 mg is supplied as Carton containing two (2) blister packages (NDC 69547-353-02) each with a single spray device.

NARCAN Nasal Spray is not made with natural rubber latex.

16.2 Storage and Handling

Store NARCAN Nasal Spray in the blister and cartons provided.

Store below 77°F (25°C). Excursions permitted up to 104°F (40°C). Do not freeze or expose to excessive heat above 104°F (40°C). Protect from light.

NARCAN Nasal Spray freezes at temperatures below 5°F (-15°C). If this happens, the device will not spray. If NARCAN Nasal Spray is frozen and is needed in an emergency, do NOT wait for NARCAN Nasal Spray to thaw. Get emergency medical help right away. However, NARCAN Nasal Spray may be thawed by allowing it to sit at room temperature

for 15 minutes, and it may still be used if it has been thawed after being previously frozen.

17 PATIENT COUNSELING INFORMATION

Advise the patient and family members or caregivers to read the FDA-approved patient labeling (*Patient Information* and *Instructions for Use*).

Recognition of Opioid Overdose

Inform patients and their family members or caregivers about how to recognize the signs and symptoms of an opioid overdose such as the following:

- Extreme somnolence - inability to awaken a patient verbally or upon a firm sternal rub.
- Respiratory depression - this can range from slow or shallow respiration to no respiration in a patient who is unarousable.
- Other signs and symptoms that may accompany somnolence and respiratory depression include the following:
    - Miosis.
    - Bradycardia and/or hypotension.

Risk of Recurrent Respiratory and Central Nervous System Depression

Instruct patients and their family members or caregivers that, since the duration of action of most opioids may exceed that of NARCAN Nasal Spray, they must seek immediate emergency medical assistance after the first dose of NARCAN Nasal Spray and keep the patient under continued surveillance *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Limited Efficacy for/with Partial Agonists or Mixed Agonist/Antagonists

Instruct patients and their family members or caregivers that the reversal of respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and may require higher doses of naloxone hydrochloride or repeated administration of NARCAN Nasal Spray, using a new nasal spray each time *[see Dosage and Administration (2.3), Warnings and Precautions (5.2)]*.

Precipitation of Severe Opioid Withdrawal

Instruct patients and their family members or caregivers that the use of NARCAN Nasal Spray in patients who are opioid dependent may precipitate opioid withdrawal *[see Warnings and Precautions (5.3), Adverse Reactions (6)]*.

Administration Instructions

Instruct patients and their family members or caregivers to:

- Ensure NARCAN Nasal Spray is present whenever persons may be intentionally or accidentally exposed to an opioid overdose (i.e., opioid emergencies).
- Administer NARCAN Nasal Spray as quickly as possible if a patient is unresponsive and an opioid overdose is suspected, even when in doubt, because prolonged respiratory depression may result in damage to the central nervous system or

death. **NARCAN Nasal Spray is not a substitute for emergency medical care** *[see Dosage and Administration (2.1)]*.
- Lay the patient on their back and administer NARCAN Nasal Spray into one nostril while providing support to the back of the neck to allow the head to tilt back *[see Dosage and Administration (2.1)]*.
- Use each nasal spray only one time *[see Dosage and Administration (2.1)]*.
- Turn patient on their side as shown in the *Instructions for Use* and call for emergency medical assistance immediately after administration of the first dose of NARCAN Nasal Spray. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance *[see Dosage and Administration (2.1)].*
- Monitor patients and re-administer NARCAN Nasal Spray using a new NARCAN Nasal Spray every 2 to 3 minutes, if the patient is not responding or responds and then relapses back into respiratory depression. Administer NARCAN Nasal Spray in alternate nostrils with each dose *[see Dosage and Administration (2.1)]*.
- Replace NARCAN Nasal Spray before its expiration date.

NARCAN® is a registered trademark licensed by Emergent Operations Ireland Limited.

Distributed by Emergent Devices Inc., Plymouth Meeting, PA 19462 USA.

PATIENT INFORMATION
NARCAN (nar´ kan)
(naloxone hydrochloride)
Nasal Spray

You and your family members or caregivers should read this Patient Information leaflet before an opioid emergency happens. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about NARCAN Nasal Spray?

NARCAN Nasal Spray is used to temporarily reverse the effects of opioid medicines. The medicine in NARCAN Nasal Spray has no effect in people who are not taking opioid medicines. Always carry NARCAN Nasal Spray with you in case of an opioid emergency.

1. Use NARCAN Nasal Spray right away if you or your caregiver think signs or symptoms of an opioid emergency are present, even if you are not sure, because an opioid emergency can cause severe injury or death. Signs and symptoms of an opioid emergency may include:
    - unusual sleepiness and you are not able to awaken the person with a loud voice or by rubbing firmly on the middle of their chest (sternum)
    - breathing problems including slow or shallow breathing in someone difficult to awaken or who looks like they are not breathing
    - the black circle in the center of the colored part of the eye (pupil) is very small, sometimes called "pinpoint pupils," in someone difficult to awaken
2. Family members, caregivers, or other people who may have to use NARCAN Nasal Spray in an opioid emergency should know where NARCAN Nasal Spray is stored and how to give NARCAN before an opioid emergency happens.
3. **Get emergency medical help right away after giving the first dose of**

NARCAN Nasal Spray. Rescue breathing or CPR (cardiopulmonary resuscitation) may be given while waiting for emergency medical help.

4. The signs and symptoms of an opioid emergency can return after NARCAN Nasal Spray is given. If this happens, give another dose after 2 to 3 minutes using a new NARCAN Nasal Spray and watch the person closely until emergency help is received.

What is NARCAN Nasal Spray?

- NARCAN Nasal Spray is a prescription medicine used for the treatment of an opioid emergency such as an overdose or a possible opioid overdose with signs of breathing problems and severe sleepiness or not being able to respond.
- NARCAN Nasal Spray is to be given right away and does not take the place of emergency medical care. Get emergency medical help right away after giving the first dose of NARCAN Nasal Spray, even if the person wakes up.
- NARCAN Nasal Spray is safe and effective in children for known or suspected opioid overdose.

Who should not use NARCAN Nasal Spray?
Do not use NARCAN Nasal Spray if you are allergic to naloxone hydrochloride or any of the ingredients in NARCAN Nasal Spray. See the end of this leaflet for a complete list of ingredients in NARCAN Nasal Spray.

What should I tell my healthcare provider before using NARCAN Nasal Spray?
Before using NARCAN Nasal Spray, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems
- are pregnant or plan to become pregnant. Use of NARCAN Nasal Spray may cause withdrawal symptoms in your unborn baby. Your unborn baby should be examined by a healthcare provider right away after you use NARCAN Nasal Spray.
- are breastfeeding or plan to breastfeed. It is not known if NARCAN Nasal Spray passes into your breast milk.

Tell your healthcare provider about the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use NARCAN Nasal Spray?
Read the "Instructions for Use" at the end of this Patient Information leaflet for detailed information about the right way to use NARCAN Nasal Spray.

- Use NARCAN Nasal Spray exactly as prescribed by your healthcare provider.
- Each NARCAN Nasal Spray contains only 1 dose of medicine and cannot be reused.
- NARCAN Nasal Spray comes in a 2 mg and 4 mg strength. Your healthcare provider will prescribe the one that is right for you.
- Lay the person on their back. Support their neck with your hand and allow the head to tilt back before giving NARCAN Nasal Spray.
- NARCAN Nasal Spray should be given into one nostril.
- If additional doses are needed, give NARCAN Nasal Spray in the other nostril.

What are the possible side effects of NARCAN Nasal Spray?
NARCAN Nasal Spray may cause serious side effects, including:

1. **Sudden opioid withdrawal symptoms.** In someone who has been using opioids regularly, opioid withdrawal symptoms can happen suddenly after receiving NARCAN Nasal Spray and may include:

- o body aches
- o diarrhea
- o increased heart rate
- o fever
- o runny nose
- o sneezing
- o goose bumps
- o sweating
- o yawning
- o nausea or vomiting
- o nervousness
- o restlessness or irritability
- o shivering or trembling
- o stomach cramping
- o weakness
- o increased blood pressure

In infants under 4 weeks old who have been receiving opioids regularly, sudden opioid withdrawal may be life-threatening if not treated the right way. Signs and symptoms include: seizures, crying more than usual, and increased reflexes.
These are not all of the possible side effects of NARCAN Nasal Spray. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NARCAN Nasal Spray?

- Store below 77°F (25°C).
- Excursions permitted up to 104°F (40°C).
- Do not freeze or expose to excessive heat above 104°F (40°C).'
- Keep NARCAN Nasal Spray in its box until ready to use. Protect from light.
- Replace NARCAN Nasal Spray before the expiration date on the box.

Keep NARCAN Nasal Spray and all medicines out of the reach of children.

General information about the safe and effective use of NARCAN Nasal Spray.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NARCAN Nasal Spray for a condition for which it was not prescribed. You can ask your pharmacist or healthcare provider for information about NARCAN Nasal Spray that is written for health professionals.

What are the ingredients in NARCAN Nasal Spray?
Active ingredient: naloxone hydrochloride
Inactive ingredients: benzalkonium chloride (preservative), disodium ethylenediaminetetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH and sterile water
NARCAN Nasal Spray is not made with natural rubber latex.
Distributed by Emergent Devices Inc., Plymouth Meeting, PA 19462 USA.
For more information, go to www.narcan.com or call 1-844-4NARCAN (1-844-462-7226).

This Patient Information has been approved by the U.S. Food and Drug Administration.
Issued: 11/2020

Instructions for Use
NARCAN (nar´ kan)
(naloxone hydrochloride)

Nasal Spray

You and your family members or caregivers should read the Instructions for Use that comes with NARCAN Nasal Spray before using it. Talk to your healthcare provider if you and your family members or caregivers have any questions about the use of NARCAN Nasal Spray.

Use NARCAN Nasal Spray for known or suspected opioid overdose in adults and children.

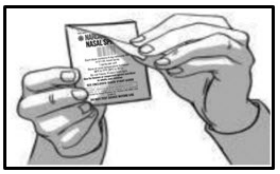
Important: For use in the nose only.

- **Do not remove or test the NARCAN Nasal Spray until ready to use.**
- **Each NARCAN Nasal Spray has 1 dose and cannot be reused.**
- **You do not need to prime NARCAN Nasal Spray.**

How to use NARCAN Nasal Spray:

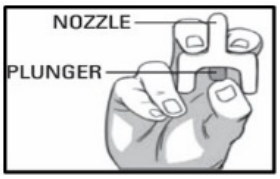
Step 1. Lay the person on their back to receive a dose of NARCAN Nasal Spray.

Step 2. Remove NARCAN Nasal Spray from the box. Peel back the tab with the circle to open the NARCAN Nasal Spray.



Note: NARCAN Nasal Spray freezes at temperatures below 5°F (-15°C). If this happens, the device will not spray. Get emergency medical help right away if this happens. Do not wait for NARCAN Nasal Spray to thaw. NARCAN Nasal Spray may still be used if it has been thawed after being previously frozen.

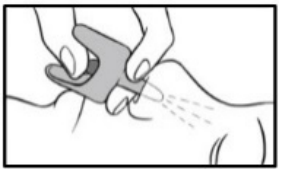
Step 3. Hold the NARCAN Nasal Spray with your thumb on the bottom of the red plunger and your first and middle fingers on either side of the nozzle.



Step 4. Tilt the person's head back and provide support under the neck with your hand. Gently insert the tip of the nozzle into **one nostril** until your fingers on either side of the nozzle are against the bottom of the person's nose.

Step 5. Press the red plunger firmly to give the dose of NARCAN Nasal Spray.

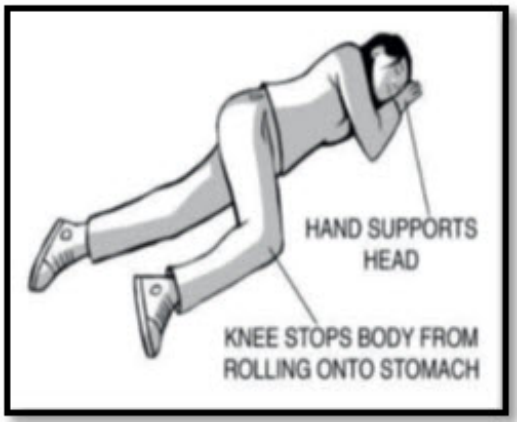
Step 6. Remove the NARCAN Nasal Spray from the nostril after giving the dose.



What to do after NARCAN Nasal Spray has been used:

Step 7. Get emergency medical help right away.

- Move the person on their side (recovery position) after giving NARCAN Nasal Spray.
- Watch the person closely.
- If the person does not respond by waking up, to voice or touch, or breathing normally another dose may be given. NARCAN Nasal Spray may be dosed every 2 to 3 minutes, if available.



- Repeat **Steps 2 through 6** using a new NARCAN Nasal Spray to give another dose in the other nostril. If additional NARCAN Nasal Sprays are available, Steps 2 through 6 may be repeated every 2 to 3 minutes until the person responds or emergency medical help is received.

Step 8. Put the used NARCAN Nasal Spray back into its box.

Step 9. Throw away (dispose of) the used NARCAN Nasal Spray in a place that is away from children.

How should I store NARCAN Nasal Spray?

- Store below 77°F (25°C).
- Excursions permitted up to 104°F (40°C).
- Do not freeze or expose to excessive heat above 104°F (40°C).
- Keep NARCAN Nasal Spray in the box until ready to use. Protect from light.
- Replace NARCAN Nasal Spray before the expiration date on the box.

Keep NARCAN Nasal Spray and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by Emergent Devices Inc. Plymouth Meeting, PA 19462 USA.

For more information, go to www.narcan.com or call 1-844-4NARCAN (1-844-462-7226).

Issued: 11/2020

PRINCIPAL DISPLAY PANEL - 2 mg Vial Package

NDC 69547-212-04
0.1 mL intranasal spray per unit
For use in the nose only
Rx Only

NARCAN®(naloxone HCl)
NASAL SPRAY 2 mg

Use NARCAN® Nasal Spray for known or suspected opioid overdose in adults and children.

Important: For use in the nose only.

Do not remove or test the NARCAN® Nasal Spray until ready to use.

This box contains four (4) 2-mg doses of naloxone HCl in 0.1 mL of nasal spray.

Four Pack

CHECK PRODUCT EXPIRATION DATE BEFORE USE.

PRINCIPAL DISPLAY PANEL - 4 mg Vial Package

NDC 69547-353-02
0.1 mL intranasal spray per unit
For use in the nose only
Rx Only

NARCAN®(naloxone HCl)
NASAL SPRAY 4 mg

Use NARCAN® Nasal Spray for known or suspected opioid overdose in adults and children.

Important: For use in the nose only.

Do not remove or test the NARCAN® Nasal Spray until ready to use

This box contains two (2) 4-mg doses of naloxone HCl nasal spray

Two Pack

CHECK PRODUCT EXPIRATION DATE BEFORE USE.

OPEN HERE FOR QUICK START GUIDE
Opioid Overdose Response Instructions

PRINCIPAL DISPLAY PANEL - 4 mg Vial Package

For use in the nose only
NDC 69547-353-02

Rx Only

NARCAN®(naloxone HCl)
NASAL SPRAY 4 mg

1 spray per device

Each dose contains 4 mg naloxone HCl
(equivalent to 3.6 mg naloxone) in 0.1 mL nasal spray
Store below 77°F (25°C).
Excursions permitted up to 104°F (40°C).
Do not freeze or expose to excessive heat
above 104°F (40°C). Protect from light.
Use for known or suspected opioid overdose
in adults and children
SEE ENCLOSED QUICK START GUIDE

LOT_XXXXXX_EXP_MMM_YYYY

Distributed by Emergent Devices Inc.
Plymouth Meeting, PA 19462 USA

DO NOT TEST DEVICE BEFORE USE

PRINCIPAL DISPLAY PANEL

NARCAN® (naloxone HCl) NASAL SPRAY

QUICK START GUIDE

Opioid Overdose Response Instructions

Use NARCAN® (naloxone hydrochloride) Nasal Spray for known or suspected opioid overdose in adults and children.

Important: For use in the nose only.

Do not remove or test the NARCAN Nasal Spray until ready to use.

1 Identify Opioid Overdose and Check for Response

Ask person if he or she is okay and shout name.

Shake shoulders and firmly rub the middle of their chest.

Check for signs of an opioid overdose:

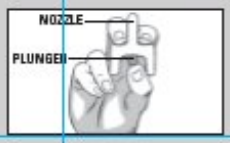
- Will not wake up or respond to your voice or touch
- Breathing is very slow, irregular, or has stopped
- Center part of their eye is very small, sometimes called "pinpoint pupils"

Lay the person on their back to receive a dose of NARCAN Nasal Spray.

2 Give NARCAN Nasal Spray

REMOVE NARCAN Nasal Spray from the box.
Peel back the tab with the circle to open the NARCAN Nasal Spray.

Hold the NARCAN Nasal Spray with your thumb on the bottom of the red plunger and your first and middle fingers on either side of the nozzle.



Gently insert the tip of the nozzle into either nostril.

- Tilt the person's head back and provide support under the neck with your hand. Gently insert the tip of the nozzle into **one nostril**, until your fingers on either side of the nozzle are against the bottom of the person's nose.

Press the red plunger firmly to give the dose of NARCAN Nasal Spray.

- Remove the NARCAN Nasal Spray from the nostril after giving the dose.

3 Call for emergency medical help, Evaluate, and Support

Get emergency medical help right away.

Move the person on their side (recovery position) after giving NARCAN Nasal Spray.

Watch the person closely.

If the person does not respond by waking up, to voice or touch, or breathing normally another dose may be given. NARCAN Nasal Spray may be dosed every 2 to 3 minutes, if available.

Repeat Step 2 using a new NARCAN Nasal Spray to give another dose in the other nostril. If additional NARCAN Nasal Sprays are available, repeat step 2 every 2 to 3 minutes until the person responds or emergency medical help is received.

For more information about NARCAN Nasal Spray, go to www.narcan.com, or call 1-844-4NARCAN (1-844-462-7226).
You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

emergent biosolutions

 A1142

NARCAN

naloxone hydrochloride spray

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69547-212
Route of Administration	NASAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NALOXONE HYDROCHLORIDE (UNII: F850569PQR) (NALOXONE - UNII:36B82AMQ7N)	NALOXONE HYDROCHLORIDE	2 mg in 0.1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
WATER (UNII: 059QF0KO0R)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69547-212-04	4 in 1 PACKAGE	01/24/2017	
1		0.1 mL in 1 VIAL, SINGLE-DOSE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:69547-212-24	24 in 1 PACKAGE	01/24/2017	
2		0.1 mL in 1 VIAL, SINGLE-DOSE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208411	01/24/2017	

NARCAN

naloxone hydrochloride spray

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69547-353
Route of Administration	NASAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NALOXONE HYDROCHLORIDE (UNII: F850569PQR) (NALOXONE - UNII:36B82AMQ7N)	NALOXONE HYDROCHLORIDE	4 mg in 0.1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
WATER (UNII: 059QF0KO0R)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69547-353-02	2 in 1 PACKAGE	01/24/2017	
1		0.1 mL in 1 VIAL, SINGLE-DOSE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208411	01/24/2017	

Labeler - Emergent Devices Inc. (079673287)

Revised: 11/2020 Emergent Devices Inc.

APPENDIX II SUMMARY OF NARCAN PHARMACOLOGY, EFFICACY, AND SAFETY

1 SUMMARY OF NARCAN PHARMACOLOGY, EFFICACY, AND SAFETY

1.1 Summary of Naloxone Pharmacology

The active pharmaceutical ingredient of NARCAN is naloxone HCl (naloxone). Naloxone HCl is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity. Naloxone has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of physical dependence on opioids, naloxone will produce withdrawal symptoms. Opiate withdrawal symptoms may appear within minutes of naloxone administration and will subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of naloxone and to the degree and type of opioid dependence.

While the mechanism of action of naloxone is not fully understood, *in vitro* evidence suggests that naloxone antagonizes opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the CNS, with the greatest affinity for the mu receptor. Naloxone is approximately 45% protein bound, primarily to albumin. Based on literature, naloxone undergoes direct glucuronidation to naloxone 3-glucoronide as well as N-dealkylation, and reduction of the 6-oxo group.

When naloxone HCl is administered IV, the onset of action is generally apparent within 2 minutes, with a duration of 45 to 90 minutes; the onset of action is slightly less rapid when it is administered SC or IM, within approximately 15 minutes. In the pivotal pharmacokinetic (PK) study comparing IM and IN administration (see Section 1.1.1), the t_{max} of the two routes of administration were equivalent of the two routes of administration were equivalent (approximately 0.33 hours) and the half-life of the IN route was longer than that of the injected naloxone. Since the duration of action of naloxone may be shorter than that of some opiates, the effects of the opiate may return as the effects of naloxone dissipate. The requirement for repeat doses of naloxone, however, will also be dependent upon the amount, type, and route of administration of the opioid being antagonized.

1.1.1 Definitive Pharmacokinetic Bridging Study

To support the development of NARCAN, one pivotal comparative PK BA study (Naloxone-Ph1a-002) was conducted in 30 healthy volunteers. This PK study was included in the original NDA for nasal naloxone (NARCAN, NDA 208411).

In this study, the relative BA of one nasal spray in one nostril, consisting of a 2 mg total dose (0.1 mL of 20 mg/mL naloxone HCl solution) and a 4 mg total dose (0.1 mL of 40 mg/mL naloxone HCl solution), and two nasal sprays administered as one nasal spray in each nostril, consisting of a 4 mg total dose (0.1 mL of 20 mg/mL naloxone HCl solution in each nostril)

and an 8 mg total dose (0.1 mL of 40 mg/mL naloxone HCl solution in each nostril), were compared to a single dose of 0.4 mg naloxone HCl intramuscular (IM) injection. For IN administration, the subjects were instructed not to breathe through the nose during administration of the nasal spray and remained fully supine for approximately one hour postdose. For IM administration, naloxone was administered as a single injection in the gluteus maximus muscle. The PK parameters obtained in the study are shown in Table 8.

In summary the PK from one IN spray in one nostril (4 mg total dose, 0.1 mL of 40 mg/mL) and one intranasal spray in each nostril (8 mg total dose, 0.1 mL of 40 mg/mL in each nostril) was compared to the reference 0.4 mg IM single-dose injection. The PK parameters obtained in the study are shown in Table 8.

Table 8 Mean Pharmacokinetic Parameters (CV%) for Naloxone Following NARCAN (Naloxone HCl) Nasal Spray and Intramuscular Injection of Naloxone HCl to Healthy Subjects

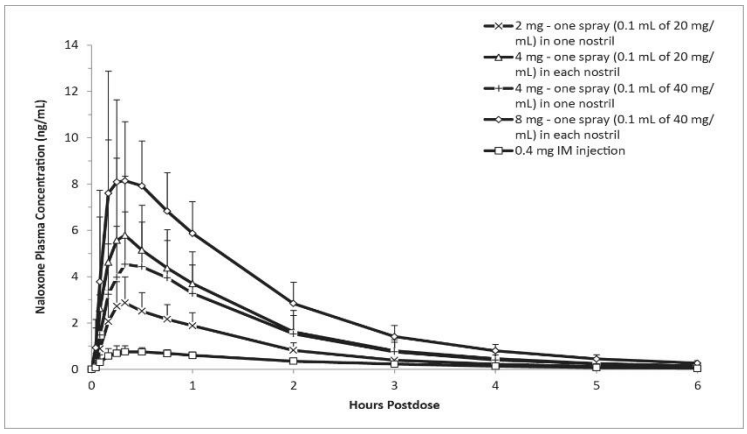
Parameter	2 mg– One Nasal Spray in one nostril 20 mg/ml (N=29)	4 mg – Two Nasal Sprays, one in each nostril 20 mg/ml (N=29)	4 mg – One Nasal Spray in one nostril 40 mg/ml (N=29)	8 mg – Two Nasal Sprays, one in each nostril 40 mg/ml (N=29)	0.4 mg Intramuscular Injection (N=29)
t_{max} (h)[†]	0.33 (0.25, 1.00)	0.33 (0.17, 0.57)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{max} (ng/mL)	2.91 (35)	6.30 (34)	4.83 (43)	9.70 (36)	0.88 (31)
AUCt (hr ng/mL)	4.60 (27)	9.64 (24)	7.87 (37)	15.3 (23)	1.75 (23)
$AUC_{0\text{-}inf}$ (h*ng/mL)	4.66 (27)	9.74 (24)	7.95 (37)	15.5 (23)	1.79 (23)
t½ (h)	1.85 (33)	2.19 (33)	2.08 (30)	2.10 (32)	1.24 (26)
Dose normalized Relative BA (%) vs. IM	51.7 (22)	54.0 (23)	44.2 (31)[††]	43.1 (24)	100

[†] t_{max} reported as median (minimum, maximum)
[††] N=28 for Relative BA.
Source: NARCAN USPI Section 12.3

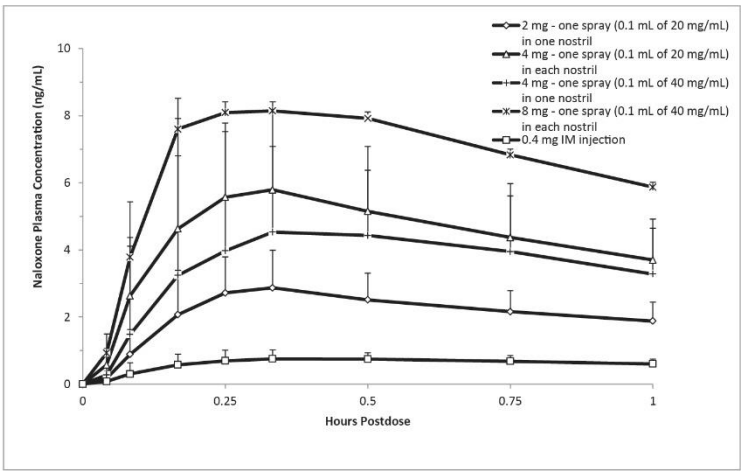
The median naloxone t_{max} after IN administration of nasal naloxone (one nasal spray in one nostril (2 mg or 4 mg) or two nasal sprays as one spray in each nostril (4 mg or 8 mg) was not significantly different compared to the 0.4 mg dose of naloxone HCl IM (Figure 5)

Figure 5 Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection

(a)



(b)



Source: NARCAN USPI Section 12.3

The dose normalized relative BA of one dose (2 mg or 4 mg) or two doses (4 mg or 8 mg) of nasal naloxone as compared to the 0.4 mg dose of naloxone HCl administered by IM injection was 52%, 44%, 54%, and 43%, respectively.

The overall conclusion from PK analysis is that nasal naloxone can deliver a dose of naloxone IN that is approximately 50% bioavailable. As such, a 4 mg IN dose will provide a dose that is equivalent to the most common IM dose of 2 mg injected. The t_{max} is approximately the same as injectable naloxone indicating that time to onset will be similar.

1.2 Summary of Efficacy

NARCAN is supported by the efficacy of the approved IM naloxone HCl (Narcan for injection) in addition to literature.

No efficacy studies have been conducted with nasal naloxone. The BA of IN naloxone has been shown to be approximately 50% of that of IM administration (see Section 1.1.1), which suggests that the IN route of administration of naloxone can be considered as effective as the parenteral route. The literature supports that the most effective and most often used out-of-hospital dose of naloxone by the IM or IV route of administration is 2 mg, which would be approximately equivalent to a 4 mg dose of IN naloxone. Literature also supports that IN dosing will achieve the same beneficial effect as IM or IV administration (see Section 1.2.2).

1.2.1 Consideration for Effectiveness of NARCAN in the non-hospital, community-use setting.

There is no single effective dose for all opioid overdoses. Many, often unknown, factors determine an adequate dose. These factors include opioid related factors such as the specific opioid(s) consumed, the opioid dose/formulation, administration mode, and concurrent medications taken (e.g., benzodiazepines); patient related factors, such as underlying diseases (e.g., respiratory illnesses), opioid tolerance, genetic make-up of the patient, and exogenous stimulatory factors; and naloxone related factors (dose and formulation) (see also Section 1.3.8.2 for a safety review of Lack of Efficacy).

As such, it is not possible to select an appropriate naloxone dose in advance of an overdose event. Therefore, in the community, pre-hospital setting, it is important that any naloxone product intended for use in non-medical settings be administered as a fixed efficacious dose to ensure that the optimal initial dose is administered as quickly as possible. In addition, emergency treatment using naloxone needs to be delivered using a method that is easily and rapidly administered by a non-trained lay person.

NARCAN is designed to be used in a non-medical, community setting. It is administered as a fixed efficacious dose thereby ensuring that the optimal initial dose is administered as quickly as possible.

The reliability of the device has met FDA guidelines. Device reliability was assessed during the original NARCAN NDA 208411. To support the switch to OTC, additional human factors testing has been performed (refer to Section 3.2). The product is supplied with two devices. In the event that the person does not respond with the first dose, another dose may be given using the second device. NARCAN device failure is assessed during ongoing safety surveillance and is described in Section 4.4).

NARCAN is indicated for repeat dosing in adults and pediatrics (per USPI, NARCAN has no maximum dosage). If the patient does not respond or responds and then relapses into respiratory depression after the initial dose, additional doses of NARCAN may be given every 2 to 3 minutes until emergency medical assistance arrives.

Use of the IN route may decrease layperson and EMS personnel exposures to bloodborne pathogens.

Expanding access to OTC NARCAN in the community setting, enables anyone to safely, rapidly, and readily administer a dose that achieves a consistently adequate initial exposure to bridge to medical care.

1.2.2 Summary Literature Review of Intranasal Naloxone Efficacy

Literature studies of IN naloxone include a prospective randomized controlled trial by Kerr et al. (2009). In this study, IN naloxone (2 mg/mL - total dose of 2 mg) reversed heroin overdose successfully in 82% of patients. Time to adequate response was the same when given IN or IM.

Merlin et al. (2010) showed that in 344 cases of opioid overdose, 2 mg IN naloxone was statistically as effective as IV naloxone at reversing the effects of opioid overdose The

aim of the study was to determine if IN naloxone administration was preferable to IV naloxone by EMS for opioid overdoses and to establish if IN naloxone was as effective as IV naloxone, but without the risk of needle exposure. A retrospective chart review of pre-hospital advanced life support patients was performed on confirmed opioid overdose patients. Initial and final unassisted respiratory rates (RR) and Glasgow Coma Scale (GCS), recorded by paramedics, were used as indicators of naloxone effectiveness. The median changes in RR and GCS were determined. Of confirmed opioid overdoses, change in RR was 6 for the IV group and 4 for the IN group ($p = 0.08$). Change in GCS was 4 for the IV group and 3 for the IN group ($p = 0.19$). Correlations between RR and GCS for initial, final, and change were significant at the 0.01 level ($p = 0.577, 0.462, 0.568$, respectively). The study concluded that IN naloxone was statistically as effective as IV naloxone at reversing the effects of opioid overdose. The IV and IN groups had similar average increases in RR and GCS. Based on the results, IN naloxone is a viable alternative to IV naloxone while posing less risk of needle stick injury (Merlin et al., 2010).

Barton et al. (2002) studied the prehospital administration of 2 mg IN (concentration 1 mg/mL) In their cohort of 30 patients, 11 (37%) responded to naloxone. Ten patients required only a single dose of IN naloxone with an average response time of 3-4 minutes (Barton et al., 2002).

In addition, pre-hospital providers are at increased risk for blood-borne exposure and disease due to the nature of their environment. The use of IN medications in high-risk populations may limit this risk of exposure. To determine the efficacy of IN naloxone in the treatment of suspected opiate overdose patients in the pre-hospital setting, Barton et al. (2005) conducted a prospective, nonrandomized trial of administering IN naloxone by paramedics to patients with suspected opiate overdoses over a 6-month period was performed All adult patients encountered in the pre-hospital setting as suspected opiate overdose, found down, or with altered mental status that met the criteria for naloxone administration were included in the study. Intranasal naloxone (2 mg) was administered immediately upon patient contact and before IV insertion and administration of IV naloxone (2 mg). Patients were then treated by EMS protocol. The main outcome measures were: time of IN naloxone administration, time of IV naloxone administration, time of appropriate patient response as reported by paramedics (Barton et al., 2005).

Ninety-five patients received IN naloxone and were included in the study. A total of 52 patients responded to naloxone by either IN or IV, with 43 (83%) responding to a 2 mg dose of IN naloxone alone. Seven patients (16%) in this group required further doses of IV naloxone. The authors concluded that IN naloxone is a novel alternative method for drug

administration in high-risk patients in the prehospital setting with good overall effectiveness. The use of this route is further discussed in relation to efficacy of treatment and minimizing the risk of bloodborne exposures to EMS personnel.

Kelly et al. (2005) conducted a prospective, randomized, open-label trial of either 2 mg IM naloxone or 2 mg IN naloxone with 155 patients (71 IM and 84 IN) requiring treatment for suspected opiate overdose. The primary outcome measure was to determine the effectiveness of IN naloxone compared with IM naloxone for treatment of respiratory depression due to suspected opiate overdose in the prehospital setting; response time to regain a respiratory rate greater than 10 per minute. Secondary outcome measures were proportion of patients with respiratory rate greater than 10 per minute at 8 minutes and/or a GCS score over 11 at 8 minutes; proportion requiring rescue naloxone; rate of adverse events; proportion of the IN group for whom IN naloxone alone was sufficient treatment. The IM group had more rapid response than the IN group and were more likely to have more than 10 spontaneous respirations per minute within 8 minutes (82% v 63%; p = 0.0173). There was no statistically significant difference between the IM and IN groups for needing rescue naloxone (13% [IM group] v 26% [IN group]; *P*= 0.0558). There were no major adverse events. For patients treated with IN naloxone, this was sufficient to reverse opiate toxicity in 74%. Intranasal naloxone was effective in treating opiate-induced respiratory depression. The authors concluded that intranasal delivery of naloxone could reduce the risk of needle stick injury to ambulance officers and, being relatively safe to make more widely available, could increase access to life-saving treatment in the community.

Robertson et al. (2009) conducted a study to compare the pre-hospital time intervals from patient contact and medication administration to clinical response for IN versus IV naloxone in patients with suspected narcotic overdose This was a retrospective review of EMS and hospital records, before and after implementation of a protocol for administration of intranasal naloxone by the Central California EMS Agency. They included patients with suspected narcotic overdose treated in the pre-hospital setting over 17 months, between March 2003 and July 2004. Paramedics documented dose, route of administration, and positive response times using an electronic record. Clinical response was defined as an increase in respiratory rate (breaths/min) or GCS score of at least 6. Main outcome variables included time from medication to clinical response and time from patient contact to clinical response. Secondary variables included numbers of doses administered and rescue doses given by an alternate route. Between-group comparisons were accomplished using t-tests and chi-square tests as appropriate. One hundred fifty-four (154) patients met the inclusion criteria, including 104 treated with IV and 50 treated with IN naloxone. Clinical response was noted in 33 (66%) and 58 (56%) of the IN and IV groups, respectively (p = 0.3). The mean time between naloxone administration and clinical response was longer for the IN group (12.9 vs. 8.1 minutes, p = 0.02). However, the mean times from patient contact to clinical response were not significantly different between the IN and IV groups (20.3 vs. 20.7 min, p = 0.9). More patients in the IN group received two doses of naloxone (34% vs. 18%, p = 0.05), and three patients in the IN group received a subsequent dose of IV or IM naloxone. The time from dose administration to clinical response for naloxone was longer for the IN route, but the overall time from patient contact to response was the same for the IV and IN routes. The authors concluded that given the difficulty and potential hazards in obtaining IV

access in many patients with narcotic overdose, IN naloxone appears to be a useful and potentially safer alternative.

1.3 Summary of Safety

The safety of NARCAN was demonstrated in a PK study (see Section 1.1) as part of the original New Drug Application (NDA 208411). NDA 208411 relies on the previous findings of safety submitted in NDA 016636 for the reference listed drug, naloxone HCl for injection.

NARCAN has over six years of safety data which remains consistent with the established product labeling. NARCAN 4 mg has been licensed in the US since 18 November 2015 and introduced to the market in February 2016. Subsequently licensure in Canada (CA) was achieved in 2016. Currently exposure to NARCAN from product launch (2016) through October 2022 is estimated to be approximately 44 million devices distributed (where one device distributed represents one dose administered).

There have been no new safety signals identified since market authorization. This includes findings specific to the target population or the route of administration. The patient benefit-risk ratio is well established.

NARCAN has no maximum dosage per approved USPI; therefore, it can be dosed repeatedly every 2-3 minutes until the patient responds with return of respirations or emergency medical services arrives. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists nasal naloxone exhibits essentially no pharmacologic activity.

This section will review the safety data from the pivotal clinical study, the post-marketing data, summary of worldwide data as it relates to naloxone class safety and targeted safety topics, including acute opioid withdrawal.

1.3.1 NARCAN Safety in Clinical Studies

The pivotal PK study Ph1a-002 enrolled a total of 30 healthy adult male and female volunteers. The aim of the study was to compare the BA of the IN formulation of naloxone to the generic form of Narcan (IM naloxone). The study design was an inpatient, open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover study involving 30 healthy volunteers (see Section 1.1.1).

The safety and tolerability of intranasal naloxone hydrochloride was adequately demonstrated in the Ph1a-002 (N=30) clinical trial.

There were no SAEs, significant events, or deaths reported in the clinical study. One subject was discontinued because of elevated blood pressure measurements on the day prior to dosing of the second treatment period (NARCAN USPI, Appendix I).

In the Ph1a-002 study, the most frequent naloxone-related AEs experienced over all doses/routes were increased blood pressure, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, and nasal inflammation.

1.3.2 NARCAN Post-Marketing Safety Experience (All Ages (Pediatric and Adults)

NARCAN has over six years of post-marketing safety data, and the safety data may be received from any source including consumers, healthcare professionals, medical and product inquiries, scientific literature. All valid safety information is entered into the Emergent pharmacovigilance safety database (Argus).

Post-marketing surveillance also includes the review of data from public regulatory agencies such as the FDA Adverse Event Reporting System (FAERS) and the World Health Organization (WHO) International Drug Monitoring Program (VigiBase).

There are limitations that effect the post-market surveillance, collection and follow up of adverse event information such as:

- Under-reporting due to the target population who may be afraid of legal consequences related to reporting of illicit substances or drug misuse.
- Lack of the ability to obtain medical confirmation; events are often reported by non-healthcare professionals
- Spontaneously received reports from consumers generally describe events that are likely related to the underlying abuse or misuse of opioids or opioid withdrawal and not related to the use of NARCAN
- Missing reporter or patient information impeding the ability to collect further case safety information

1.3.3 Extent of Post-Marketing Exposure

Currently, NARCAN is primarily distributed to wholesalers, pharmacies, police departments, public schools, and universities/college within the US and CA. NARCAN is not always distributed directly to end user, therefore, the best estimate to calculate patient exposure is by using the distribution data. Based on the distribution data to US and CA through October 2022, patient exposure is estimated to be approximately 44 million doses (devices). It should be noted that since multiple doses can be repeated as often as necessary, patient exposure can only be estimated.

1.3.4 Post-Marketing Adverse Events

Since the time of US licensure in November 2015 to present, the adverse events reported have been consistent with the product labelling which include generalized symptoms consistent with the effects of abrupt reversal of analgesic effects and/or withdrawal syndrome.

Sources of safety data include spontaneous reports, reports from literature, and regulatory authorities. For the period of 01JAN2016 through 30JUN2021 (included in the supplemental Integrated Safety Summary (ISS) submitted in the NARCAN sNDA), 397 individual case safety reports have been received from postmarketing sources containing 902 events in the Emergent pharmacovigilance safety database. Of the 397 ICSRs, there were 93 serious ICSRs reporting 332 SAEs. The comprehensive review of safety identified the primary

demographic for use of NARCAN are comprised of adults in the in the 18-65 year-old age group (55.4%)

Table 9 summarizes the number of adverse events occurring in each system organ class (SOC) (>2%) reported by age groups (per supplemental ISS submitted in the NARCAN sNDA). More than 26% of all the adverse events were reported in the General disorders and administration site conditions, 15% of the events occurred in the Injury, poisoning, and procedural complications class, and 13.5% of the events were in the Psychiatric disorders class.

Table 9 Common Events by System Organ Class (≥ 2%) – Categorized by Age Groups

MedDRA v25.0 System Organ Class (SOC)	< 2 years n=1	2 to < 18 years n=25	18 to < 65 years n=495	65 years and older n=76	Unknown n=224	Total N=812
General disorders and administration site conditions	0	7	142	17	69	235 (28.9)
Injury, poisoning, and procedural complications	0	4	61	17	53	135 (16.6)
Psychiatric disorders	0	1	82	1	38	122 (15.0)
Nervous system disorders	0	5	83	11	14	113 (13.9)
Gastrointestinal disorders	0	2	52	6	25	85 (10.5)
Respiratory, thoracic, and mediastinal disorders	0	1	25	2	6	34 (4.2)
Investigations	1	2	11	10	9	33 (4.1)
Cardiac disorders	0	3	11	2	3	19 (2.3)
Infections and infestations	0	0	9	9	0	18 (2.2)
Musculoskeletal and connective tissue disorders	0	0	10	1	7	18 (2.2)

Source: Table 3 in Supplemental ISS - Emergent (ARGUS) Safety Database Analysis

Table 10 provides the adverse events that occurred in greater than 2% of cases regardless of seriousness (per Supplemental ISS submitted in the NARCAN sNDA). The most frequently reported adverse event was drug withdrawal syndrome (PT), comprising of a total of 76 events (8.4% of all the adverse events). In addition, 51 events of unintentional use for unapproved indication were received (5.7% of all the events). The events reported were consistent with the established safety profile of NARCAN as listed in the USPI.

Table 10 Common Adverse Events (>2%) – by Age Group

MedDRA v25.0 Preferred Term (PT)	< 2 years n=0 (0)	2 to < 18 years n=3 (1.2)	18 to < 65 years n=143 (58.8)	65 years and older n=12 (4.9)	Unknown n=85 (35.0)	Total N=243 (n%)
Drug withdrawal syndrome	0	0	53	2	21	76 (31.3)
Unintentional use for unapproved indication	0	1	22	7	21	51 (20.1)
Vomiting	0	1	26	0	15	42 (17.3)
Drug ineffective	0	0	17	1	9	27 (11.1)
Feeling abnormal	0	0	11	2	12	25 (10.3)
Anger	0	1	14	0	7	22 (9.1)
Total	0	3	141	12	87	243

Source: Table 4 in Supplemental ISS - Emergent (ARGUS) Safety Database Analysis

1.3.5 Post-Marketing Serious Adverse Events

A summary tabulation of all SAEs categorized by SOC and PT and age group are provided in Table 11 (per Supplemental ISS submitted in the NARCAN sNDA).

Of these, SOCs occurring in greater than 5% included:

- Nervous system disorders (18.7%)
- General disorders and administration site conditions (17.5%)
- Psychiatric disorders (10%)
- Injury, poisoning and procedural complications (8.8%)
- Gastrointestinal disorders (7.3%)
- Respiratory, thoracic, and mediastinal disorders (6%)
- Investigations (5.7%)

From 01JAN2016 through 30JUN2021, a total of 62 SAEs were reported and subsequently coded to the SOC Nervous System Disorders. The SAEs included but were not limited to 12 events of seizure, 7 events of loss of consciousness, and 5 events of unresponsive to stimuli. The events reported are consistent with the USPI and/or known effects of opioids. Most of the adverse events reported in this SOC are consistent with the underlying opioid overdose or opioid withdrawal.

Of the total SAEs (N= 332), the SAEs reported in >2% of the total SAEs, were death (4.2%), drug ineffective (2.7%), drug withdrawal syndrome (3.6%), loss of consciousness (2.1%), seizure (3.6%), refer to Table 11. However, most of the serious cases are considered related to the underlying opioid overdose or withdrawal.

1.3.6 World-Wide Data Review

A comprehensive review of safety information from the FDA FAERS and WHO Vigibase databases included an analysis of adverse events, serious outcomes, and fatal cases categorized by the route of administration (i.e., intranasal, non-nasal and unknown) and age group (i.e., 0-<2, 2-<18, 18-<65, 65+).

The route of administration was not specified by the reporter in most reports. Out of those reports with information on route of administration, the analysis did not identify an increase in adverse events or serious outcomes with intranasal use.

1.3.7 Use in Special Populations

Use of naloxone in special populations, such as pregnant, pediatric, geriatric, renal/hepatic impaired, or nasal mucosal impaired individuals is documented in the Emergent pharmacovigilance safety database. Spontaneous reporting has not yielded a sufficient number of reports (i.e., limited number of cases reported for pregnancy exposure and pediatric use from 01JAN2016 to 30JUN2021, with only 4 and 8 cases, respectively) to analyze the use of NARCAN in special populations. Nonetheless, the anticipated benefits of naloxone in suspected overdose are expected to outweigh any potential risks in all populations.

1.3.8 Targeted Safety Topics

1.3.8.1 Acute Opioid Withdrawal

Drug withdrawal syndrome occurs due to abrupt discontinuation of drugs in individuals who have a dependence on the substrate and is generally not life threatening. Drug withdrawal syndrome is a group of various symptoms experienced because of rapid depletion of opioid in a user; the symptoms are variable, and may include body aches, pain, fever, asthenia, seizures, restlessness, irritability, aggressive behavior, nausea, increased blood pressure, and tachycardia. In neonates, opioid withdrawal may be life-threatening including death if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes. The severity of drug withdrawal syndrome will depend on the degree of physical dependence, the dose and potency of the opioid that induced the overdose, and the dose of naloxone administered. The limited content of naloxone per spray helps prevent the administration of an inadvertently high dose of naloxone and its increased risk of acute opioid withdrawal. Reports of acute opioid withdrawal in the Emergent safety database is very low, with 27 serious cases cumulatively out of approximately 27 million doses (reporting frequency of 0.1 per 100,000 doses distributed; Supplemental ISS).

A review of the FAERS database identified 190 serious cases with withdrawal symptoms identified. There were 364 serious cases with withdrawal symptoms identified in the Vigibase dataset.

Instructions defined in the labeling to administer repeat doses of NARCAN, as necessary every 2 to 3 minutes if the patient does not respond or responds and then relapses, along with the limited content of naloxone per spray (0.1 mL) helps reduce the risk of acute opioid withdrawal.

The quantitative and qualitative review of acute opioid withdrawal in the Emergent's pharmacovigilance safety database, FAERS database, and Vigibase database did not identify any unexpected findings including meaningful differences in the route of administration. The relative severity of the reported events above has been moderate to low due to nonserious outcomes.

Events reported were consistent quantitively and qualitatively with the known effects of NARCAN administration in the setting of opioid abuse and were consistent with the USPI and/or known effects of opioids as most reported AEs are consistent with the underlying overdose or withdrawal. The benefit of NARCAN treatment outweighs the risk of opioid withdrawal syndrome.

Awareness of the possibility of acute withdrawal syndrome after administration of naloxone is important. To this effect, instructions to request emergency medical assistance encourage laypersons to call for professional help as well as to be aware of the possibility of this effect.

1.3.8.2 Lack of Efficacy

Naloxone is an opioid antagonist with higher affinity to the opioid receptors that competes and displaces opioids at opioid receptor sites; thus, the effectiveness will depend on the severity of the opioid overdose. Lack of effect can be related to various factors, such as the length of time from symptom onset to initial treatment and the pharmacodynamics of the competing opioid, device malfunction, product availability at the time of the overdose and medication errors. The requirement for repeat doses of NARCAN depends upon the amount, type, and route of administration of the opioid being antagonized.

If the desired response is not obtained after 2 or 3 minutes, an additional dose of NARCAN using a new NARCAN should be administered. If there is still no response and additional doses are available, additional doses of NARCAN should be administered every 2 to 3 minutes using a new NARCAN with each dose until emergency medical assistance arrives.

Naloxone is not effective in counteracting overdoses due to barbiturates, benzodiazepines, psychostimulants (e.g., cocaine, amphetamines, methylphenidate, etc.), alcohol, or any other non-opioid drug such as non-opioid tranquilizers, anesthetics or sedatives. NARCAN can be administered to an unconscious person suspected of having an opioid overdose and may not have beneficial effect.

Cases of lack of effect (LOE) have been reported for naloxone HCl, across all databases, the lowest number of cases of LOE were reported for the intranasal route. Most cases of LOE reported for NARCAN reported limited information and may have been confounded with rebound toxicity. Lack of efficacy events were reported in 10 serious cases cumulatively (reporting frequency of 0.04 per 100,000 doses administered) in the safety database. The FAERS Database identified 90 unique serious cases with lack of efficacy events identified.

The Vigibase Database identified 68 unique serious cases with lack of efficacy events identified.

The overall effectiveness of NARCAN as it relates to the reversal of opioid overdose is dependent upon many factors including: severity of the overdose, use of synthetic drugs, number of doses administered, patient positioning and most important, the time lapse when administered from the time of overdose. An increase in frequency and severity have not been observed in the identified and potential risks for the product which support the effectiveness of the current risk minimization measures in place. There are no trends to directly link the adverse events from drug ineffective to NARCAN administration.

1.3.8.3 Risk of limited efficacy with Partial Agonists or Mixed Agonist/Antagonists

Per the approved NARCAN USPI, reversal of respiratory depression by agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses of naloxone or additional doses of NARCAN should not be considered as lack of effect. Buprenorphine has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

1.3.8.4 Rebound opioid toxicity

The duration of action of most opioids may exceed that of nasal naloxone and result in a relapse of the respiratory and/or central nervous system depression after an initial improvement in symptoms, which may be confounded as lack of effect.

1.3.8.5 Medication Error and Device Failure

A medical device is any device intended to be used for medical purposes. All medical devices run the risk of occasional malfunction or failure. It is recognized that as a device, there is potential for failure to actuate nasal naloxone. Device failure is mitigated in the packaging configuration. The product carton contains 2 doses in the unlikely event a failure occurred on the first. Device failure was reported in 6 nonserious cases cumulatively (reporting frequency of 0.02 per 100,000 doses administered) in the safety database and an assessment of the reported data does not change the benefit-risk profile of the product.

Cases of medication error and other product use errors and issues have been reported for naloxone HCl, across all databases. Medication error events were reported in 11 unique serious cases cumulatively (reporting frequency of 0.04 per 100,000 doses administered) in the safety database, 91 unique serious cases in the FAERS database, and 46 unique serious cases in the Vigibase database with events identifying medication error events. An assessment of the reported data presents a minimal risk for nasal naloxone.

The quantitative and qualitative review of potential user error in the Emergent's safety database, FAERS database, and Vigibase database did not identify any unexpected findings including meaningful differences in the route of administration. The risk of death due to opioid overdose is far greater than the risk of having naloxone administered unnecessarily.

Events of this nature are closely monitored for trends, including increases in frequency and severity during all routine stages of pharmacovigilance activities such as signal detection, aggregate reporting, and risk management. The overall analysis does not change the benefit-risk profile of the product.

1.3.9 Safety Surveillance – Pharmacovigilance Activities

Emergent pharmacovigilance activities for NARCAN are compliant with the US Federal regulations for combination products.

Routine pharmacovigilance activities performed by the Emergent PV department include:

- Adverse event reporting – database and medical review of individual case safety reports
- Periodic Benefit-Risk Evaluation Report (PBRER)
- Signal detection activities - including the review of world-wide safety data with the use of Empirica Signal ™ and comprehensive literature review

1.3.10 Benefit-Risk Assessment of Safety Profile

Emergent Pharmacovigilance monitors safety information both quantitatively and qualitatively in real-time and in aggregate during routine pharmacovigilance activities and signal detection. On an annual basis, Emergent submits a PBRER that provides a thorough analysis of safety information including identified and potential risks to ensure that risk minimization including product labeling is adequate to ensure safety and efficacy of the product. To date, the safety information received under NDA 208411 (NARCAN) remains consistent with the known safety profile of naloxone and target population (i.e., known, or suspected opioid overdose).

From the time of market authorization to present, Emergent has not identified any trends or increased risks associated with the intranasal administration of the product.

NARCAN continues to have a favorable benefit-risk profile for the emergency treatment of known or suspected opioid overdose and for the proposed non-prescription (OTC) setting.

1.3.11 Serious Events by SOC and PT by Age

Adverse event data received from spontaneous sources, including literature and regulatory authority reports, are tabulated below by SOC and PT categorized by age group for the period of 01JAN2016 through 30JUN2021 (per supplemental ISS submitted in NARCAN sNDA). A total of 93 serious ICSRs reporting 332 serious adverse events have been collected and assessed.

Table 11 Serious Events by SOC and PT by Age Group

System Organ Class **Preferred Term**	**Child[a]** **N=1** **n(%)**	**Adolescent[b]** **N=22** **n(%)**	**Adult[c]** **N=206** **n(%)**	**Elderly[d]** **N=56** **n(%)**	**UNK[e]** **N=47** **n(%)**	**Grand Total** **N=332** **n(%)**
Nervous system disorders	**n=0**	**n=5 (22.7)**	**n=42 (20.8)**	**n=9 (16.1)**	**n=6 (11.8)**	**n=62 (18.7)**
Amnesia	0	0	2	0	0	2
Balance disorder	0	0	1	0	0	1
Brain injury	0	2	0	0	1	3
Burning sensation	0	0	1	0	0	1
Cerebrovascular accident	0	0	1	0	0	1
Cognitive disorder	0	0	2	0	0	2
Depressed level of consciousness	0	0	2	0	0	2
Dizziness	0	0	2	0	0	2
Drug withdrawal convulsions	0	0	1	1	0	2
Dysstasia	0	0	0	0	1	1
Exaggerated startle response	0	0	0	0	1	1
Generalised tonic-clonic seizure	0	0	1	0	0	1
Headache	0	0	2	0	0	2
Hypoaesthesia	0	0	1	0	0	1
Hypoxic-ischaemic encephalopathy	0	1	0	0	0	1
Lethargy	0	0	2	1	0	3
Loss of consciousness	0	0	6	1	0	7
Memory impairment	0	0	2	1	0	3
Metabolic encephalopathy	0	0	0	1	0	1
Monoplegia	0	0	0	1	0	1
Nerve compression	0	0	0	1	0	1
Presyncope	0	0	1	0	0	1
Ruptured cerebral aneurysm	0	0	1	0	0	1
Seizure	0	1	9	0	2	12
Somnolence	0	0	1	0	0	1
Syncope	0	0	1	0	0	1
Transient ischaemic attack	0	1	0	0	0	1
Tremor	0	0	0	0	1	1
Unresponsive to stimuli	0	0	3	2	0	5
General disorders and administration site conditions	**n=1 (100)**	**n=5 (23.8)**	**n=35 (17.3)**	**n=2 (3.6)**	**n=15 (29.4)**	**n=58 (17.5)**
Asthenia	0	0	2	0	0	2

System Organ Class **Preferred Term**	**Child[a]** **N=1** **n(%)**	**Adolescent[b]** **N=22** **n(%)**	**Adult[c]** **N=206** **n(%)**	**Elderly[d]** **N=56** **n(%)**	**UNK[e]** **N=47** **n(%)**	**Grand Total** **N=332** **n(%)**
Brain death	0	1	0	0	1	2
Crying	0	0	1	0	0	1
Death	0	0	5	0	9	14
Drug effective for unapproved indication	1	0	0	0	0	1
Drug ineffective	0	0	6	0	3	9
Drug ineffective for unapproved indication	0	2	1	0	0	3
Drug withdrawal syndrome	0	0	12	0	0	12
Fatigue	0	0	1	0	0	1
Feeling abnormal	0	0	0	0	1	1
Gait disturbance	0	0	0	0	1	1
Gait inability	0	0	1	0	0	1
Hyperthermia	0	1	0	0	0	1
Illness	0	0	1	0	0	1
Injection site pain	0	0	0	1	0	1
Malaise	0	0	1	0	0	1
Pain	0	0	0	1	0	1
Pyrexia	0	1	1	0	0	2
Terminal state	0	0	1	0	0	1
Unevaluable event	0	0	2	0	0	2
Psychiatric disorders	**n=0**	**n=0**	**n=29 (14.4)**	**n=0**	**n=4 (7.8)**	**n=33 (10.0)**
Abnormal behaviour	0	0	3	0	0	3
Aggression	0	0	1	0	1	2
Agitation	0	0	1	0	1	2
Anxiety	0	0	2	0	0	2
Anxiety disorder	0	0	1	0	0	1
Depressed mood	0	0	1	0	0	1
Depression	0	0	1	0	0	1
Disorientation	0	0	1	0	0	1
Drug dependence	0	0	5	0	0	5
Dysphemia	0	0	0	0	1	1
Eating disorder	0	0	1	0	0	1
Insomnia	0	0	2	0	0	2
Lack of spontaneous speech	0	0	2	0	0	2

System Organ Class **Preferred Term**	**Child[a]** **N=1** **n(%)**	**Adolescent[b]** **N=22** **n(%)**	**Adult[c]** **N=206** **n(%)**	**Elderly[d]** **N=56** **n(%)**	**UNK[e]** **N=47** **n(%)**	**Grand Total** **N=332** **n(%)**
Mood altered	0	0	2	0	0	2
Nervousness	0	0	1	0	0	1
Personality change	0	0	1	0	0	1
Psychotic behaviour	0	0	1	0	0	1
Psychotic disorder	0	0	1	0	1	2
Substance abuse	0	0	1	0	0	1
Tachyphrenia	0	0	1	0	0	1
Injury, poisoning and procedural complications	**n=0**	**n=2** **(9.5)**	**n=15** **(7.2)**	**n=6** **(10.7)**	**n=6** **(13.6)**	**n=29** **(8.8)**
Contusion	0	0	0	1	0	1
Fall	0	0	1	1	1	3
Incorrect route of product administration	0	0	1	0	1	2
Maternal exposure during pregnancy	0	0	0	0	1	1
Off label use	0	0	1	0	0	1
Overdose	0	0	3	2	0	5
Poisoning	0	0	0	1	0	1
Product prescribing issue	0	0	1	0	0	1
Product selection error	0	0	0	0	1	1
Road traffic accident	0	0	1	0	0	1
Toxicity to various agents	0	2	3	0	1	6
Traumatic lung injury	0	0	1	0	0	1
Unintentional use for unapproved indication	0	0	2	1	1	4
Wrong technique in product usage process	0	0	1	0	0	1
Gastrointestinal disorders	**n=0**	**n=1** **(4.8)**	**n=17** **(8.1)**	**n=5** **(8.9)**	**n=1** **(2.3)**	**n=24** **(7.3)**
Abdominal discomfort	0	0	1	0	0	1
Abdominal distension	0	0	1	0	0	1
Abdominal pain	0	0	0	1	0	1
Abdominal pain upper	0	0	0	0	1	1
Anal incontinence	0	0	1	0	0	1
Barrett's oesophagus	0	0	0	1	0	1
Diarrhoea	0	0	1	1	0	2
Dry mouth	0	0	1	0	0	1

System Organ Class **Preferred Term**	**Child[a]** **N=1** **n(%)**	**Adolescent[b]** **N=22** **n(%)**	**Adult[c]** **N=206** **n(%)**	**Elderly[d]** **N=56** **n(%)**	**UNK[e]** **N=47** **n(%)**	**Grand Total** **N=332** **n(%)**
Gastric disorder	0	0	1	0	0	1
Gastrointestinal haemorrhage	0	0	0	1	0	1
Nausea	0	0	2	0	0	2
Oesophageal disorder	0	0	0	1	0	1
Oesophageal food impaction	0	0	1	0	0	1
Pancreatitis	0	0	1	0	0	1
Rectal haemorrhage	0	1	0	0	0	1
Retroperitoneal haematoma	0	0	1	0	0	1
Vomiting	0	0	6	0	0	6
Respiratory, thoracic, and mediastinal disorders	**n=0**	**n=1** **(4.8)**	**n=14** **(6.9)**	**n=1** **(1.8)**	**n=4** **(7.8)**	**n=20** **(6.0)**
Acute respiratory distress syndrome	0	0	1	0	0	1
Acute respiratory failure	0	0	1	0	0	1
Chronic obstructive pulmonary disease	0	0	1	0	0	1
Cough	0	0	1	0	0	1
Dyspnoea	0	0	2	0	0	2
Nasal congestion	0	0	1	0	0	1
Non-cardiogenic pulmonary oedema	0	0	1	0	0	1
Oropharyngeal pain	0	0	0	1	0	1
Pneumonitis aspiration	0	0	2	0	1	3
Pulmonary oedema	0	0	1	0	0	1
Respiration abnormal	0	0	0	0	1	1
Respiratory arrest	0	0	1	0	0	1
Respiratory depression	0	0	1	0	0	1
Respiratory failure	0	1	1	0	2	4
Investigations	**n=0**	**n=2** **(9.5)**	**n=6** **(3.0)**	**n=9** **(16.1)**	**n=2** **(3.9)**	**n=19** **(5.7)**
Blood creatinine increased	0	0	1	0	0	1
Blood culture positive	0	0	0	3	0	3
Blood pressure increased	0	0	2	0	0	2
Electrocardiogram QT prolonged	0	1	0	0	0	1
Electrocardiogram ST segment abnormal	0	1	0	0	0	1
Haematocrit decreased	0	0	0	2	0	2

System Organ Class **Preferred Term**	**Child[a]** **N=1** **n(%)**	**Adolescent[b]** **N=22** **n(%)**	**Adult[c]** **N=206** **n(%)**	**Elderly[d]** **N=56** **n(%)**	**UNK[e]** **N=47** **n(%)**	**Grand Total** **N=332** **n(%)**
Haemoglobin decreased	0	0	1	2	0	3
Heart rate decreased	0	0	0	1	0	1
Heart rate increased	0	0	0	0	1	1
Pulse absent	0	0	0	0	1	1
Respiratory rate decreased	0	0	1	0	0	1
Weight decreased	0	0	1	0	0	1
White blood cell count decreased	0	0	0	1	0	1
Infections and infestations	**n=0**	**n=0**	**n=7** **(3.3)**	**n=9** **(16.1)**	**n=0**	**n=16** **(4.8)**
Cholecystitis infective	0	0	0	1	0	1
COVID-19	0	0	1	0	0	1
Infection	0	0	1	0	0	1
Meningitis	0	0	1	0	0	1
Oral candidiasis	0	0	0	2	0	2
Pneumonia	0	0	1	0	0	1
Pneumonia aspiration	0	0	1	0	0	1
Pseudomonas infection	0	0	0	2	0	2
Sepsis	0	0	0	1	0	1
Septic shock	0	0	1	0	0	1
Spinal cord abscess	0	0	1	0	0	1
Streptococcal infection	0	0	0	2	0	2
Urinary tract infection	0	0	0	1	0	1
Cardiac disorders	**n=0**	**n=3** **(14.2)**	**n=8** **(3.8)**	**n=2** **(3.5)**	**n=2** **(4.5)**	**n=15** **(4.5)**
Arrhythmia	0	0	1	0	0	1
Atrial fibrillation	0	0	0	2	0	2
Bradycardia	0	1	1	0	0	2
Cardiac arrest	0	1	3	0	1	5
Cardiac failure	0	0	1	0	0	1
Cardiac failure congestive	0	0	1	0	0	1
Cardio-respiratory arrest	0	0	0	0	1	1
Extrasystoles	0	1	0	0	0	1
Left ventricular dysfunction	0	0	1	0	0	1
Musculoskeletal and connective tissue disorders	**n=0**	**n=0**	**n=7** **(3.5)**	**n=1** **(1.7)**	**n=1** **(1.9)**	**n=9** **(2.7)**
Arthralgia	0	0	2	0	1	3

System Organ Class **Preferred Term**	**Child[a]** **N=1** **n(%)**	**Adolescent[b]** **N=22** **n(%)**	**Adult[c]** **N=206** **n(%)**	**Elderly[d]** **N=56** **n(%)**	**UNK[e]** **N=47** **n(%)**	**Grand Total** **N=332** **n(%)**
Back pain	0	0	0	1	0	1
Lumbar spinal stenosis	0	0	1	0	0	1
Myalgia	0	0	1	0	0	1
Pain in jaw	0	0	1	0	0	1
Rheumatoid arthritis	0	0	2	0	0	2
Metabolism and nutrition disorders	**n=0**	**n=1** **(4.7)**	**n=5** **(2.4)**	**n=1** **(1.8)**	**n=0**	**n=7** **(2.1)**
Dehydration	0	0	0	1	0	1
Diabetes mellitus	0	0	2	0	0	2
Hyperkalaemia	0	0	1	0	0	1
Hypokalaemia	0	1	1	0	0	2
Lactic acidosis	0	0	1	0	0	1
Hepatobiliary disorders	**n=0**	**n=0**	**n=2** **N=1.0**	**n=3** **N=5.3**	**n=1** **N=1.9**	**n=6** **N=1.8**
Biliary colic	0	0	1	0	0	1
Cholelithiasis	0	0	0	1	0	1
Gallbladder disorder	0	0	0	1	0	1
Gallbladder enlargement	0	0	0	1	0	1
Gallbladder hypofunction	0	0	0	0	1	1
Liver injury	0	0	1	0	0	1
Renal and urinary disorders	**n=0**	**n=1** **(4.7)**	**n=3** **(1.4)**	**n=1** **(1.7)**	**n=1** **(16.7)**	**n=6** **(1.8)**
Acute kidney injury	0	1	1	0	0	2
Renal failure	0	0	1	1	0	2
Renal impairment	0	0	0	0	1	1
Renal pain	0	0	1	0	0	1
Vascular disorders	**n=0**	**n=1** **(4.8)**	**n=4** **(2.0)**	**n=1** **(1.7)**	**n=0** **N=0**	**n=6** **N=1.8**
Cyanosis	0	0	1	0	0	1
Hypertension	0	0	1	0	0	1
Hypotension	0	1	1	1	0	3
Shock haemorrhagic	0	0	1	0	0	1
Skin and subcutaneous tissue disorders	**n=0**	**n=0**	**n=2** **(1.0)**	**n=3** **(5.3)**	**n=0** **(0)**	**n=5** **(1.5)**
Acute 68eneralized exanthematous pustulosis	0	0	0	2	0	2

System Organ Class Preferred Term	Child[a] N=1 n(%)	Adolescent[b] N=22 n(%)	Adult[c] N=206 n(%)	Elderly[d] N=56 n(%)	UNK[e] N=47 n(%)	Grand Total N=332 n(%)
Hyperhidrosis	0	0	1	0	0	1
Pustular psoriasis	0	0	0	1	0	1
Rash	0	0	1	0	0	1
Immune system disorders	**n=0**	**n=0**	**n=2 (0.99)**	**n=1 (1.7)**	**n=2 (3.6)**	**n=5 (1.5)**
Anaphylactic shock	0	0	0	0	1	1
Cytokine storm	0	0	1	0	0	1
Drug hypersensitivity	0	0	1	1	0	2
Hypersensitivity	0	0	0	0	1	1
Blood and lymphatic system disorders	**n=0**	**n=0**	**n=1 (0.5)**	**n=2 (3.5)**	**n=0**	**n=3 (0.9)**
Disseminated intravascular coagulation	0	0	1	0	0	1
Febrile neutropenia	0	0	0	2	0	2
Product issues	**n=0**	**n=0**	**n=2 (1.0)**	**n=0**	**n=1 (1.9)**	**n=3 (0.9)**
Device malfunction	0	0	1	0	0	1
Device occlusion	0	0	1	0	0	1
Product quality issue	0	0	0	0	1	1
Social circumstances	**n=0**	**n=0**	**n=2 (1.0)**	**n=0**	**n=0**	**n=2 (0.6)**
Impaired driving ability	0	0	1	0	0	1
Loss of personal independence in daily activities	0	0	1	0	0	1
Ear and labyrinth disorders	**n=0**	**n=0**	**n=1 (0.5)**	**n=0**	**n=0**	**n=1 (0.3)**
Vertigo	0	0	1	0	0	1
Surgical and medical procedures	**n=0**	**n=0**	**n=1 (0.5)**	**n=0**	**n=0**	**n=1 (0.3)**
Drug detoxification	0	0	1	0	0	1
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**n=0**	**n=0**	**n=1 (0.5)**	**n=0**	**n=0**	**n=1 (0.3)**
Squamous cell carcinoma	0	0	1	0	0	1
Pregnancy, puerperium, and perinatal conditions	**n=0**	**n=0**	**n=0**	**n=0**	**n=1 (1.9)**	**n=1 (0.3)**
Premature delivery	0	0	0	0	1	1
Grand Total	**1**	**22**	**206**	**56**	**47**	**332**

N=Total number of events per category; n(%) number of occurrences and percentage of category total
[a]=Child (2 to < 12 years) [b]=Adolescent (12 to 17 years) [c]=Adult (18 to < 65 years) [d]=Elderly (65 years and older) [e]=UNK=unknown

Source: Table I: 1 Supplemental ISS- Emergent Argus Safety Database

2 REFERENCES

Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104(12):2067-2074

Merlin MA, Saybolt M, Kapitanyan R, et al. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. Am J Emerg Med. 2010;28(3):296-303.

Barton ED, Ramos J, Colwell C, Benson J, Baily J, Dunn W. Intranasal administration of naloxone by paramedics. Prehosp Emerg Care. 2002;6(1):54-58.

Barton ED, Colwell CB, Wolfe T, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. J Emerg Med. 2005;29(3):265-271.

Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Med J Aust. 2005;182(1):24-27.

Robertson TM, Hendey GW, Stroh G, Shalit M. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. Prehosp Emerg Care. 2009;13(4):512-515

FDA. Center for Drug Evaluation and Research. NDA 208411. November 18, 2015. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000SumR.pdf

APPENDIX III SUPPLEMENTAL HUMAN FACTORS INFORMATION

Emergent conducted a HF study to evaluate the ability of potential OTC user groups to follow and apply the directions for use in Step 2 on the proposed NARCAN DFL to appropriately administer nasal naloxone in a simulated opioid emergency. The results demonstrated that the HF study was successful. The lower limit of the 95% CI exceeded the pre-defined target performance thresholds for the first and second Primary Endpoints (Step 2a and Step 2b) at 90.3% (for each). While the target performance threshold of 90% was not met for the third Primary Endpoint (Step 2c) with a lower limit of the 95% CI at 86.4%, the observed proportion of correct or acceptable performance of this step was 94.4% of subjects.

As displayed in Table 4, five participants did not adequately demonstrate Step 2c. See below for a summary of their demographic characteristics, HF performance, and comprehension of the label direction.

Participant (b) (6) was a 64-year old White female who qualified as having normal literacy per the REALM and reported that she had completed "some college or technical school". Prior to the interview she had never heard of naloxone. This participant turned the mannequin on its side at the start of the demonstration in an effort to keep the airway open, which blocked the independent reviewers view of her demonstrating Steps 2a-2c on the video recording. While the on-site interviewer rated this participant as having conducted Steps 2a-2c correctly, this could not be confirmed, so the participant was conservatively not classified as having demonstrated these steps adequately. Note that there would be no clinical consequence in an actual overdose emergency if the product was administered to a person in a lateral recumbent position.

Participant (b) (6) was a 65-year-old White male who qualified as having normal literacy per the REALM and reported that he had completed "some college or technical school". This participant reported that he had used opioids in the 90 days prior to the interview, and not heard of naloxone prior to study participation. While performing Step 2c, the subject did not keep the tip of the device completely in the nostril in the appropriate cranial or superior direction. While administering the first dose, his hand slipped slightly from the correct position into more of a posterior direction at the end of administration. The tip of the device did not entirely exit the nostril, so in a real-world scenario the overdose victim would have likely still absorbed at least a partial dose through the nasal mucosa membrane. In addition, the participant properly administered a second dose, so no additional mitigation strategies were required.

Participant (b) (6) was a 16-year-old Black female who had completed her sophomore year in high school and qualified as having normal literacy per the REALM-Teen test (it is noted that she missed the maximum number of words allowed by the test to still be considered normal literacy). This participant reported that she had not heard of naloxone prior to study participation. While performing Step 2c, the participant appeared to have squeezed the plunger rather than depressing it (i.e., similar to how one would squeeze a dropper), resulting in no dose being administered. The participant did not hold the device properly, gripping the bottom of the device with one hand and squeezing the plunger with the other. This participant's video was re-reviewed in detail. Based on the verbal exchange

between the participant and interviewer, the participant's comments during the HF demonstration indicated that they were unsure that a dose had been delivered. During re-review of the LC, it was determined that their answer was not referring to "squeezing" the device, i.e., putting pressure on the plunger while stabilizing the top with her other fingers, but squeezing the actual plunger itself. As a result, the scoring for this LC question, which was originally scored as correct, was updated to be scored as "incorrect". However, because interviewer prematurely debriefed after the participant gave their initial response, not enough information was gathered to determine the root cause of their confusion. Given that during the HF demonstration the participant indicated they were unsure a dose had been delivered and they were the only participant to demonstrate this behavior, with the other mitigations strategies that are already in place, like calling 911, it was determined that no additional mitigation strategies were necessary.

Participant (b) (6) was a 17-year-old White male who had completed his freshman year in high school and qualified as having normal literacy per the REALM-Teen test. This participant reported that he had not heard of naloxone prior to study participation. During the HF demonstration, the participant opened the blister pack but did not attempt to actually administer a dose and was rated as incorrect for all primary endpoints. This participant's video was re-reviewed in detail. The participant placed the bottom of the plunger in the nostril and verbally stated that at that point he would dispense the dose, but that he couldn't because there was no liquid. The interviewer then prematurely debriefed the participant on what they did wrong, after the HF demonstration but before the LC questions. The participant assumed for unknown reasons that the device was not functional and thus he did not attempt to truly demonstrate. This appears to be an artifact of the research setting and the participant not fully engaging with the study. Due to study artifact and the interviewer's premature debriefing, a root cause could not be determined. The participant did not attempt to use the device or give a dose, which may have cued him to his error had he tried to deliver a dose. Considering this and the other mitigations strategies already in place, like calling 911, it was determined that no additional mitigation strategies were necessary.

Participant (b) (6) was a 16-year-old White female who had completed her freshman year in high school and qualified as having normal literacy per the REALM-Teen test. This participant reported that she had not heard of naloxone prior to study participation. This participant did not understand that she should actually administer the product in the demonstration, and only verbally described how to administer nasal naloxone. Participants were given minimal directions to preserve the naturalism of the simulation and demonstration, so this was considered a research artifact that would not be an issue in an actual overdose emergency. Moreover, this subject demonstrated perfect understanding of this step when asked the label comprehension question for Step 2 and was thus classified as acceptable for this endpoint.