FDA Briefing Document

NDA/BLA# 208411

Drug name: naloxone hydrochloride nasal spray, 4 mg

Applicant: Emergent BioSolutions, Inc.

Joint Nonprescription Drug Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee Meeting

February 15, 2023

Division of Nonprescription Drugs 1/Office of Nonprescription Drugs and Division of Anesthesiology, Addiction Medicine, and Pain Medicine/Office of Neuroscience

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The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the nonprescription application for naloxone hydrochloride nasal spray to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	Advisory Committee
AE	adverse event
ARGUS	Applicant's pharmacovigilance database
AUC	area under the concentration-time curve
CC	close call
C_{max}	peak plasma concentration
CONFER	Comprehension for OTC Naloxone (Pivotal Label Comprehension Study)
COWS	Clinical Opiate Withdrawal Scale
DFL	Drug Facts Label
FAERS	FDA Adverse Events Reporting System database
FDA	Food and Drug Administration
HCl	hydrogen chloride
HCP	healthcare practitioner
HF	human factors
HFVS	human factors validation study
IM	intramuscularly
IN	intranasally
INN	intranasal naloxone
IV	intravenous
LCS	label comprehension study
LL	limited literacy
NDA	new drug application
NNS	Narcan Nasal Spray
NSP	National Sales Perspective
PDP	principal display panel
PE	point estimate
PK	pharmacokinetic
QSG	Quick Start Guide
REALM	Rapid Estimate of Adult Literacy in Medicine test
UD	use difficulty
UE	use error

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

We would like to thank the committee in advance for their participation in this joint Nonprescription Drugs Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee meeting to be held on February 15, 2023. The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss the adequacy of the data supporting Emergent Biosolutions' application to switch its product, naloxone hydrochloride (HCl) nasal spray 4 mg (Narcan Nasal Spray, NNS), from prescription to nonprescription status. Prescription NNS is currently the most commonly sold emergency treatment for opioid overdose in United States pharmacies.[1] It is approved for use to treat known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, in those of all ages, including neonates. The question at hand is whether untrained consumers can use this product safely and effectively based on the information provided by the user interface[2], including in the proposed nonprescription label, without the supervision of a health care practitioner (HCP) or other community training resource.

Naloxone HCl solution for injection has been in widespread use as an opioid reversal agent since 1971 either in the hospital or under the care of a HCP. NNS has been in use as a prescription product designed for community use since 2016. A community use treatment is administered by individuals without medical training (i.e., laypeople) in community settings without the need for additional supplies or assembly before use.

Currently, naloxone is frequently administered for community use using a variety of community based naloxone distribution programs and without a patient-specific prescription under state Naloxone Access Laws (NAL). The models of community-based naloxone distribution and NALs help to inform the potential public health benefit of nonprescription naloxone. However, despite the useful information obtained through these models, they do not necessarily inform us on whether a lay person could, on their own, safely and effectively administer NNS without the supervision of HCP by relying on the labeling (87 FR 68702, November 16, 2022). This is because community based naloxone distribution programs and state NALs may provide other instructions for use as part of a naloxone kit and patient counseling on how to use naloxone as part of the programs. Thus, these programs are not the same as nonprescription use.

As stated in 21 CFR 310.200(b), a drug originally approved as a prescription drug under section 503(b)(1)(B) of the Food, Drug, and Cosmetic Act may be switched to nonprescription status if FDA finds that the prescription requirement for such a drug is not necessary for the protection of the public health. For a drug product to switch from prescription to nonprescription status, FDA must also determine there are sufficient data demonstrating that the drug product can be used safely and effectively by consumers without the supervision of a licensed healthcare practitioner. As stated recently (87 FR 68702, November 16, 2022), a preliminary assessment of certain naloxone products – up to 4 milligrams nasal spray and up to 2 mg autoinjector may be approvable as safe and effective for nonprescription use.

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[1] Symphony Health Metys; Section 8.13.

[2] The term *user interface* refers to all components of the product with which the user interacts, including the device constituent part(s) of the product and any associated controls and displays, as well as product labels, labeling, and packaging.

The focus of this AC meeting is to discuss whether the Applicant's product, NNS, is safe and effective for nonprescription use based on the product labeling, the results of human factors (HF) testing, and findings of the postmarketing data that have accumulated for prescription NNS since its approval in 2016. We look forward to this discussion.

1.2 Context for Issues to Be Discussed at the AC

Accidental or intentional overdose and death associated with the use of illicit and/or prescription opioids is a public health crisis in the United States. More than a million people have died from drug overdose – largely opioids – in the last two decades since the Centers for Disease Control began collecting data. Deaths from opioid overdose rose from 69,061 in 2020 to 80,926 in 2021, a rise of 17.2% in 1 year (CDC 2022). Deaths occur most frequently in those ages 18 to 65 years, but occur in children as well. Between 1999 and 2016, nearly 9000 children and adolescents died from opioid poisonings (Gaither et al. 2018) with the highest annual rates among adolescents aged 15 to 19 years. Opioid overdose can occur in a patient prescribed an opioid medication, in household contacts of patients using opioids, and in people who obtain opioids illegally. Opioid overdose is characterized by life-threatening respiratory and central nervous system depression that, if not immediately treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury.

For the last 7 years, NNS has been marketed as an opioid receptor antagonist that antagonizes opioid effects by competing for the same opioid receptor binding sites. It can reverse the respiratory depression, sedation, and hypotension associated with opioid overdose. NNS has been sold in the United States and in Canada as a prescription-only fixed-dose nasal spray product for "the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression; for immediate administration as emergency therapy in settings where opioids may be present."

There are several single-ingredient naloxone products available by prescription in the United States. There are four FDA-approved presentations of naloxone prescription products: nasal sprays, injectables available in vials and ampules, prefilled syringes, and autoinjectors. Nasal sprays, in addition to NNS, include generic 4 mg products, and Kloxxado, an 8 mg product. The nasal spray formulations collectively account for the most commonly sold dosage form of naloxone (96.5% in 2021).[3] Injectable naloxone products are approved for intramuscular (IM), subcutaneous, and intravenous (IV) use, although they have been used off-label intraosseously and intranasally (IN) using a mucosal atomizer device.

In order to encourage naloxone applicants to enter the nonprescription market and to accelerate development of nonprescription naloxone, FDA took the unprecedented approach to study, develop, test and validate a model naloxone Drug Facts Label (DFL)[4] (see Figure 8). In 2018, FDA conducted the Comprehension for OTC Naloxone (CONFER) Pivotal Label Comprehension Study (LCS), to facilitate the switch of naloxone from prescription to nonprescription status. Because of the escalating opioid crisis, in August 2022, FDA Commissioner Robert Califf announced an Overdose Prevention Framework (FDA 2022a), which aims to prevent drug overdoses and deaths and includes the goal of increasing access to opioid overdose reversal agents, specifically naloxone. In keeping with these goals, FDA issued Federal Register notice (87 FR 68702, November 16, 2022). This FR notice announced the preliminary

[3] Derived from Symphony Health Metys data discussed in this review.

[4] Applicants who chose to use the FDA model DFL may add the device-specific instructions to the DFL and evaluate the proposed product in a simulated HF validation study specific to their user interface to demonstrate that the user interface could be used safely and effectively by intended users for the intended use under the expected environment(s) of use.

assessment that certain naloxone drug products—up to 4 mg nasal spray and up to 2 mg autoinjector for IM or subcutaneous use—may be approvable as safe and effective for nonprescription use pending FDA review of additional supportive information and data. Other aspects of the framework include encouraging harm reduction through education.

On September 29, 2022, Emergent Biosolutions submitted this supplementary application to switch NNS from prescription to nonprescription status. The drug product and intranasal delivery device proposed for nonprescription use are identical to the currently approved prescription product. To support the nonprescription application, Emergent Biosolutions utilized FDA's model naloxone nasal spray DFL, which was made available as part of a Federal Register notice (84 FR 8728, March 11, 2019). Applicants using FDA's model DFL would only need to test the components of the DFL that pertained to their specific product. In alignment with the FR notice, Emergent Biosolutions developed new packaging which includes carton labeling and the blister pack, Figure 10, and Figure 13) for its nonprescription naloxone product, including the addition of its product-specific DFL (see Figure 8). Emergent Biosolutions also removed the Quick Start Guide (QSG) (see Figure 16 and Figure 17) from the device blister container.

1.3 Brief Description of Issues for Discussion at the AC Meeting

To meet the approval standards for nonprescription products, an application for a nonprescription naloxone product must include sufficient data to demonstrate that consumers can appropriately select the proposed product and use it safely and effectively on themselves or on another individual suffering from opioid overdose without the supervision of an HCP. Such data may be derived from consumer studies and human factors data demonstrating appropriate selection and treatment by the consumer. The essence of nonprescription drug products is that they have the following characteristics:

- Their benefits outweigh their risks.
- Their potential for misuse and abuse is low.
- Consumers can use them for self-diagnosed conditions.
- The product can be adequately labeled to allow safe and effective use without additional instruction.
- HCPs are not required for the safe and effective use of the product.

At this AC meeting, we will focus on whether data submitted by Emergent Biosolutions are sufficient to demonstrate that the proposed nonprescription user interface can be used safely and effectively by intended users, for intended uses, under the expected environment(s) of use without the supervision of a licensed HCP. These data include results of a simulated-use human factors validation study (HFVS) designed to assess whether the user interface, including the DFL, is adequately designed to support intended users, including those with limited literacy (LL), so that they can properly use nonprescription NSS. Because naloxone is intended to be used in an emergency setting to reverse an opioid overdose, proper use and administration by the consumer is essential for efficacy in the nonprescription setting.

We ask the AC to consider the postmarketing data and pay special attention to serious adverse events included in the prescription labeling that might inform the development of nonprescription labeling. Specifically, consider cases of naloxone-induced opioid withdrawal symptoms as these may be life-threatening. Additionally, please consider instances of limited efficacy, including death, despite prescription NNS treatment which could reflect unintentional misuse, medication errors, or device failure.

Emergent Biosolutions utilized FDA's model DFL, made alterations to add product-specific information, and then tested a "mock" carton in a simulated-use HFVS with 71 participants. The study was performed without requesting comment and guidance from FDA regarding the HFVS methodology or protocol. Based on the design and methodology of the HFVS, study limitations must be taken into consideration when interpreting the study results. A more detailed discussion of each limitation is provided in Section 5.4. We ask the AC to consider these and other potential HFVS limitations with regard to the implications for consumer use. Key study limitations include:

- Pediatric users between 10 to 14 years old who may administer the proposed product to revive someone during an overdose were not tested; therefore, the data collected may not be generalized to this untested age range of the adolescent user group.
- Two user groups did not include at least 30% LL participants, which may have introduced bias with tendency towards positive performance in the affected user groups.
- Participants were allowed an unlimited familiarization period, which is not representative of the high risk scenario where users may need to act quickly, with limited time to examine product labeling during an overdose event.
- Moderators employed use of leading language and the "think aloud" method, which is not reflective of an actual use scenario and may have influenced participant behavior/performance.
- The "mock" carton labeling tested in the HFVS differs from the intend-to-market carton labeling, which may influence whether the HFVS results can be relied upon to support the intend-to-market labeling.

Because naloxone is intended to be used in an emergency setting to reverse an opioid overdose, proper use and administration by the consumer is essential for efficacy in the nonprescription setting. Based on the results of the HFVS, we would like the committee to consider whether the principal display panel (PDP) (see Figure 12), the DFL (see Figure 11), the carton (see Figure 10), blister labeling (see Figure 13), and delivery device labeling (see Figure 14) are optimized to help consumers recognize the condition of use and safely and effectively perform the steps to administer the proposed nonprescription naloxone product or whether changes to user interface are advised to further enhance safe and effective use.

Finally, we ask the AC to consider the overall packaging and labeling of NNS, other than the DFL. One issue that bears particular consideration is whether inclusion of a package insert containing the DFL instructions for use would be beneficial to include in the blister package of each device. It is possible that some consumers may not choose to keep the entire NNS box, instead carrying the NNS device in its blister packaging. If this were to occur, consumers may not have necessary directions for use in the case of an emergency.

1.4 Draft Points for Consideration

1. DISCUSSION: Discuss the safety profile for use of NNS in the nonprescription setting.
2. DISCUSSION: Discuss whether the results of the HFVS support that consumers are able to safely and effectively administer nonprescription NNS in an emergency setting with the proposed user interface. Include discussion of:
    a. Limitations of the HFVS study design and their potential effect on the interpretability of the study.
    b. Whether the design of the user interface directly contributed to the numerous errors where participants started with Step 3 (Call 911) during the simulation, bypassing Step 1 and 2, which may cause delayed treatment. Discuss the "Directions" section of the DFL

that spans over two different panels and whether the intend-to-market nonprescription carton may be further improved to mitigate risk of delayed administration.

c. Whether the Step 2 pictogram contributed to incorrect finger placement on the nasal spray in the HFVS and if the pictogram could be further improved to optimize correct administration.

d. Whether the HFVS data submitted using the "mock" nonprescription user interface support the safe and effective use of the proposed nonprescription NNS and the modified intend-to-market user interface. If not, what additional data are needed?

3. DISCUSSION: Discuss whether there is any additional labeling information that might mitigate risk of use errors.

4. VOTE: Is the benefit-risk profile for NNS supportive of its use as a nonprescription opioid overdose reversal agent?

   a. If not, what further data should be obtained?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

In the decades since an injectable formulation of naloxone was first approved in 1971, naloxone has been widely used to reverse the effects of opioids given as part of anesthesia, as well as to treat accidental or intentional poisonings with pharmaceutical opioids or illicit opioids. The increasing incidence of accidental poisonings associated with the rise in opioid use has led many community groups, public health programs, and harm reduction organizations to encourage widespread distribution of naloxone for lay administration in emergency situations. These groups often supplied an injectable formulation of naloxone (i.e., either a vial or syringe) along with a needle or mucosal atomizer device, which allowed for the injectable formulation to be delivered as an intranasal spray. However, concern over the bioavailability and appropriate dose of naloxone solution given in this way prompted FDA to encourage the development of suitable intranasal formulations. This was achieved in 2015 with the approval of NNS, the first intranasal treatment of opioid overdose for community use. At present, in addition to approved intranasal treatments other than NNS 4 mg, there are several generic intranasal naloxone (INN) products and an 8 mg nasal spray product (Kloxxado), that are all available by prescription for community use.

Some from community-based distribution programs state that FDA approval of a nonprescription naloxone product would increase access to and availability of naloxone. Some believe that having naloxone available as a nonprescription product would increase naloxone use because it would allow consumers concerned about potential stigma of opioid dependency to buy the product without hesitation or embarrassment of interacting with a pharmacist. Despite all 50 States, the District of Columbia, and Puerto Rico having passed laws and issuing standing orders enabling naloxone to be sold or distributed without a prescription, many pharmacies fail to carry the product due, in part, to issues related to the product's prescription status. This may be due to pharmacists' lack of familiarity or understanding of standing orders without a patient-specific prescription. Some pharmacists may also find the situation using a standing order burdensome. In a White Paper by Remedy Alliance For the People, (Nabarun et al. 2021) a nonprofit Buyers Club collective of over 100 harm-reduction programs who distribute naloxone directly to those who need it, they suggest that many of the barriers to wider naloxone access are attributed to naloxone's prescription status.

It is important to understand that assessing total availability and distribution of naloxone products in the United States is uniquely challenging. Naloxone is different from most prescription drug products that

are primarily distributed through the traditional wholesale pharmaceutical distribution supply chain. FDA sources estimate that approximately 5.2 million naloxone nasal spray units were sold from manufacturers to health care settings in 2021, an increase from 1.1 million units in 2017. However, these estimates do not capture donations or direct sales from manufacturers, which account for a substantial source of naloxone distribution. Some sources cite that community-based naloxone distribution programs received over two million injectable naloxone doses donated by manufacturers or purchased in bulk at low cost between 2017 and 2021 (Wheeler and Doe-Simkins 2020; Direct Relief 2021).

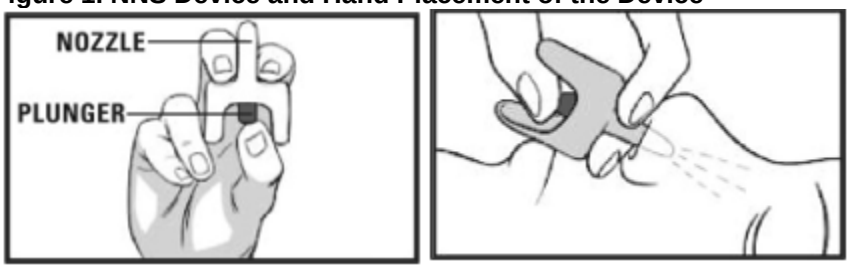
To evaluate data on the safety and efficacy of NNS, it is critical to understand the changing market of naloxone distribution and utilization in the United States, as well as issues affecting distribution, since these factors impact the accessibility of the product. The data do not explain why opioid-related deaths have continued to climb despite the increase in the distribution of the product to the community. Presumably this is related to accessibility issues including cost, the widespread use of high-potency synthetic opioids, and other social factors. Regardless, the data provide a valuable perspective on the low number of adverse events (AEs) reported for known safety concerns associated with the product, as well as the lack of newly emerging safety concerns despite the large quantities distributed.

It is important to note that sales distribution and dispensed prescription data do not provide a direct estimate of use (what is administered to individuals). Naloxone is obtained as a preventative measure and stored until use may be needed in an emergency situation. Similar to injectable epinephrine used for anaphylaxis, if naloxone is not used before the product expires, the product may end up not being used. In summary, it is unknown how access and availability of naloxone may shift with the switch from prescription to nonprescription status, but it is anticipated that a nonprescription status will remove one barrier to treatment for a life-threatening condition.

2.2 The Drug Product

NNS is a drug-device combination product that consists of 4 mg of naloxone hydrochloride in 0.1 mL aqueous solution, supplied in a single-dose nasal spray device (Figure 14). Each carton contains two NNS devices which are packaged in individual blister packs. The naloxone solution is contained in a Type I borosilicate glass vial closed with a chlorobutyl rubber plunger, which is mounted into a unit-dose nasal spray device. The device is a nonpressurized dispenser, which delivers the active ingredient. Each delivered dose contains 100 µL. Each spray is a single dose of naloxone and it cannot be reused. The device and correct hand placement for administration are shown in Figure 1. The proposed blister pack cover can be seen in Figure 13.

Figure 1. NNS Device and Hand Placement of the Device



Source: Original NDA 208411 Naloxone 4 mg Nasal Spray, approved November 2015.

In the original approval package for NNS, it is stated that the product was created to be portable and ready for use with tamper-evident features. The blister package is opened by using a peel tab. The

product was designed to be administered by a user without significant medical training. No priming of the pump is necessary.

The reliability of the drug product, naloxone hydrochloride and the spray device, was previously established at the time of the approval of NNS in 2015. As part of two postmarketing requirements to the New Drug Application (NDA), the Applicant satisfactorily established procedures for monitoring reports of failure of the drug-device combination product to activate or to deliver the full-labelled dose and confirmed that the devices were reliable. The drug product and intranasal delivery device proposed for nonprescription use are identical to the currently approved prescription product.

2.3 Clinical Basis of Efficacy and Safety for Naloxone

2.3.1 Injectable Naloxone HCl

Naloxone HCL for injection was first approved in 1971 under NDA 016636. The Summary Basis of Approval describes six clinical studies providing evidence of safety and efficacy. The studies involved various doses of naloxone given alone, before, concomitant with, or after a mu-opioid agonist. Several of the studies explored the effects of giving naloxone before or with opioids to prevent respiratory depression. Regarding those that evaluated the reversal of opioid-induced respiratory depression, the Summary Basis of Approval concludes that:

- Naloxone 5 µg/kg given 7 minutes after oxymorphine[5] 20 mg/kg, meperidine 2 mg/kg, or alphaprodine 0.66 mg/kg "adequately decreased respiratory depression."
- Naloxone 5 µg/kg given 7 minutes after morphine 0.2 to 0.3 mg/kg, oxymorphine 20 µg/kg, levorphan 50 µg/kg, meperidine 1.5 mg/kg, or fentanyl 1.5 µg/kg "prevented respiratory depression to some degree." Effects of naloxone were noted to be greater than that of nalorphine or levallorphan.
- Naloxone in doses of 0.5, 1.0, 5.0, and 10.0 mg/kg [sic] IV given after 0.75 mg/kg morphine IV; "all naloxone dosage levels reversed the morphine-induced respiratory depression."

From a safety perspective, a total of 78 healthy adult subjects were exposed to one or two doses of various doses of naloxone and dizziness, feeling hot, headache, and injection site erythema were the only AEs that occurred in more than one subject.

The original approved indication for injectable naloxone was:

> Narcan is indicated for the complete or partial reversal of narcotic depression, including respirator depression, induced by natural and synthetic narcotics[6], and the narcotic-antagonist analgesic, pentazocine. Narcan is also indicated for the diagnosis of suspected opiate overdosage.

Upon approval in 1971, labeling of the injectable product advised that "the usual initial adult dose is 0.4 mg (1 mL) Narcan administered IV, IM, or subcutaneous. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately, it may be repeated at 2-to-3-minute intervals. Failure to obtain significant improvement after two or three doses suggests that the condition

[5] Oxymorphine was the preferred terminology used for the active metabolite of oxycodone in 1971, at time of approval; currently oxymorphone is the preferred terminology for the metabolite.

[6] According to the Centers for Disease Control, narcotic drugs originally referred to any substance that dulled the senses and relieved pain. Some people use it as a term to refer to all illegal drugs, but technically, it only refers to opioids. Opioid is now the preferred term to avoid confusion. Opioids can be natural, synthetic or semi-synthetic.

may be due partly or completely to other disease processes or non-narcotic drugs." The prescribing information states, "additional supportive measures and/or resuscitative may be helpful while awaiting emergency medical services."

2.3.2 Prescription Narcan Nasal Spray Approval

After the approval of the first naloxone product, FDA established a plan for the clinical development of novel naloxone drug products relying on a pharmacokinetic (PK) standard based on FDA's finding of safety and efficacy for injectable naloxone, in lieu of conducting efficacy trials. Additionally, nonclinical studies to evaluate local toxicity were not performed for NNS given the clinical experience with intranasal naloxone, lack of any novel excipients, the acute use of the drug product, and the potentially life-saving indication.

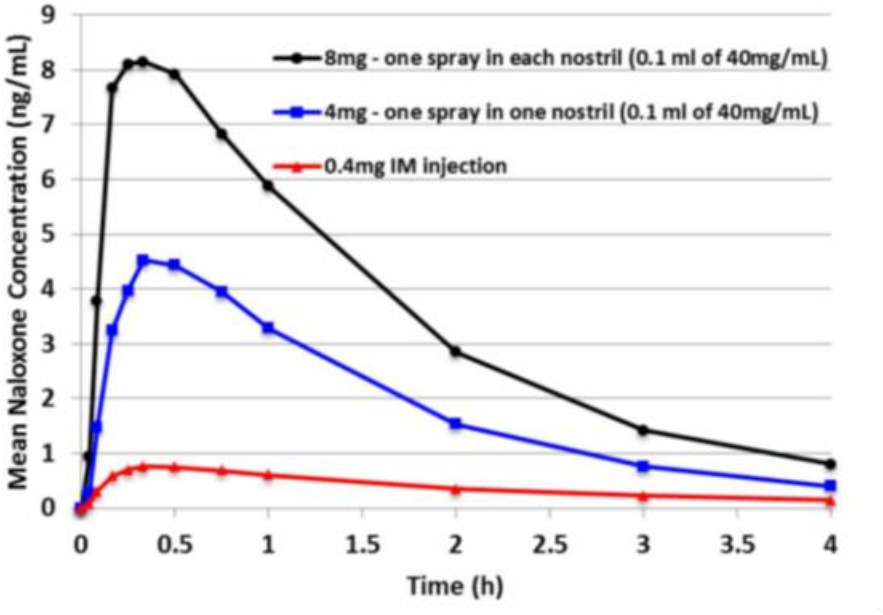
NDA 208411 for prescription Narcan nasal spray was submitted in July 2015 and was reviewed on a Priority basis.[7] Clinical trials were not performed to determine an effective dose range. The approach for establishing efficacy in novel naloxone drug products was to demonstrate comparable or greater bioavailability to an approved naloxone dose and route of administration in healthy adult volunteers along with data supporting the safety of the proposed naloxone dose. The novel naloxone drug product had to match or exceed the PK profile of the approved naloxone product, especially during the early critical period of opioid overdose when prolonged apnea could lead to permanent hypoxic brain injury or death. The key PK parameters include the peak plasma concentration (C_{max}), time to C_{max}, and systemic exposure as measured by the area under the concentration-time curve (AUC) during the first few minutes postdosing.

The comparative bioavailability studies linking or cross-referencing the 4 mg nasal spray product to the 0.4 mg IM naloxone hydrochloride solution reference product (NDA 16636) were used to establish efficacy for NNS. Since Narcan injectable solution had been discontinued from sale[8], the Applicant used a generic naloxone product manufactured by Hospira Inc., Lake Forest, Illinois, in the pivotal relative bioavailability study. Both one NNS in one nostril (i.e., 4 mg dose) and one NNS in each nostril (i.e., 8 mg dose) demonstrated much higher systemic exposure to naloxone, in terms of both AUC and C_{max} values, in comparison to the reference product. The naloxone plasma concentration-time profiles of naloxone from 0 to 4 hours following intranasal (n=30) and intramuscular (n=29) naloxone administration to healthy subjects are shown in Figure 2.

NNS exhibited a 5.5-fold higher C_{max} and 4.7-fold higher AUC_t from one spray in one nostril (4 mg total dose) and 11-fold higher C_{max} and 8.9-fold higher AUC_t from one spray in each nostril (8 mg total dose) compared to the reference, a single dose of naloxone 0.4 mg given via IM injection. Both NNS doses (one dose and two doses) demonstrated higher naloxone concentrations than the reference intramuscular product at all time points, as listed in Table 1.

[7] In 1992 under the Prescription Drug User Fee Act, FDA created a two-tiered system of review times, Standard Review and Priority Review. A Priority Review designation means that the FDA's goal is to take action on the application within 6 months (compared to 10 months under Standard Review).
[8] Discontinuation was not for reasons of safety or efficacy, as published in 74 FR 22751, May 14, 2009.

Figure 2. Mean Plasma Concentration-Time Profiles of Naloxone (IN and IM) From 0 to 4 Hours



Source: Clinical Pharmacology review of NDA 208411, 2015 original submission, p. 3.
Abbreviations: IM, intramuscularly; IN, intranasally

Table 1. Comparison of Mean Naloxone Concentrations From 2.5 to 60 Minutes Postdose

Time post-dose after naloxone drug product administration (minutes)	Mean Concentration (ng/mL) (% CV) N=29			Fold higher naloxone concentration:	Fold higher naloxone concentration:
	Reference IM injection (0.4 mg)	Test One IN spray in one nostril (4mg)	Test One IN spray in each nostril (8mg)	One IN spray (4mg) Vs. IM injection (0.4 mg)	One IN spray in each nostril (8mg) Vs. IM injection (0.4mg)
2.5	0.079 (168)	0.28 (151)	0.93(131)	3.5	11.8
5	0.306 (108)	1.48 (117)	3.78 (105)	4.8	12.3
10	0.578 (55)	3.24 (67)	7.66 (68)	5.6	13.3
15	0.696 (46)	3.97 (56)	8.10 (44)	5.7	11.6
20	0.754 (36)	4.53 (50)	8.14 (31)	6.0	10.8
30	0.749 (25)	4.43 (43)	7.92 (25)	5.9	10.6
45	0.684 (25)	3.95 (41)	6.83 (24)	5.8	10.0
60	0.604 (24)	3.28 (37)	5.87 (23)	5.4	9.7

Source: Clinical Pharmacology review of NDA 208411 2015 original submission, p. 4.
Abbreviations: CV, coefficient of variation; IM, intramuscular; IN, intranasal

FDA concluded that the PK data supported the efficacy of NNS in treating opioid overdose. Notably, because of the higher fixed dose of this product and the concern for precipitating AEs related to the reversal, additional labeling language was recommended to inform prescribers that other naloxone products that could be dosed by weight and titrated to effect were preferred for postanesthesia opioid reversal and for treatment of neonatal respiratory depression in newborns.

A similar PK evaluation was not conducted in pediatric patients. This approach to forgo clinical studies in pediatric patients was taken due to ethical and logistical concerns that precluded the conduct of studies both in healthy pediatric subjects and in pediatric patients. A PK study in healthy pediatric subjects

would be ethically challenging as enrolled subjects would have no prospect of direct benefit from receiving the drug. Conducting a controlled clinical trial in pediatric subjects with a potentially life-threatening opioid overdose would be both logistically difficult and potentially unethical due to its experimental nature in the setting of available and proven life-saving therapy (weight-based naloxone by injection). Therefore, FDA approved NNS for the full pediatric age range as the benefits of having this product available to children of all ages in the community setting were considered to far outweigh the risks. The Applicant was asked upon approval to submit both serious and nonserious outcomes as expedited reports for all children less than one year of age as well as to fulfill a postmarketing requirement that monitored underdosing and failure to dose events. Upon review of the postmarketing data, the labeling was considered adequate with no need for modification. Further details can be found in Section 3.3.7.

From the safety perspective, a limited amount of additional clinical safety data were collected to evaluate local tolerability. The AE profile demonstrated the potential for NNS to result in mild local irritation.

Additionally, because prescription NNS also represented a change in the intended use environment and users (from use in health care settings by health-care professionals to prescription use in a community setting by laypeople), a HFVS was conducted to support this context of use. The HFVS evaluated 53 untrained adults and adolescents 12 years of age and older including some limited literacy individuals who were representative of the intended user group who might administer naloxone. The HFVS results provided sufficient data to support the conclusion that NNS could be safe and effective for prescription use.

NNS 4 mg was approved on November 18, 2015 for intranasal administration of naloxone for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. The current labeling for NNS advises that for children and adults the recommended initial dose is one spray delivered into one nostril. The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized.

2.4 Presubmission Regulatory History of this Supplement

The Applicant had four meetings with FDA to discuss its nonprescription drug development program. In the earliest meeting with FDA, advice was provided to the Applicant about its development program and the data/information needed to support the proposed market conversion from prescription to nonprescription use. During the meetings, FDA noted that we do not believe that any clinically meaningful distinction exists between currently approved prescription and potential nonprescription NNS based on differences in population because in the development of the model DFL, FDA tested the labeling across a wide range of potential nonprescription naloxone users, including adults who have and have not used opioids as well as adolescents. As such, FDA recommended that the applicant pursue a full switch of NNS suitable for all users of the product rather than a partial switch.

During subsequent interactions, FDA recommended that the Applicant validate the nonprescription product user interface in a qualitative simulated-use HFVS and encouraged the Applicant to submit the study protocol for feedback before commencing the study. Specifically, regarding the Applicant's proposal to leverage label comprehension data from the model DFL, FDA responded:

> If your proposed DFL does not have additions to the FDA-tested DFL (other than the specific directions for administration), you do not need to conduct additional label comprehension studies. However, if it contains additions or changes, then it would require additional LCS assessment. In regard to human factors testing, you will need to validate your proposed DFL in a simulated qualitative human factors study utilizing the specific product intended for marketing.

Regarding the Applicant's proposal to leverage the previously collected HF data that were submitted to support the prescription application, FDA responded:

> Previous human factors testing was not conducted using the proposed DFL, so the DFL represents a new, unvalidated aspect of the user interface.

Subsequently, on September 29, 2022, the Applicant submitted its supplementary application that proposed to change the marketing status of Narcan nasal spray, 4 mg, for a full nonprescription switch.

3 Summary of Issues for the AC

3.1 Efficacy Issues

As the proposed nonprescription drug product is identical to the prescription drug product except for the DFL and packaging, some of the efficacy of naloxone and the drug device combination did not need to be reestablished, but could rely on the information gathered to support the approval of the prescription product under NDA 208411. However, the effectiveness of the product is also predicated on whether the proposed nonprescription user interface can be safely and effectively used by consumers without the supervision of a HCP. We start with the assumption that the product may be in the hands of a naïve user. The design of the entire user interface plays an important role in how effective the product is at reversing opioid-induced respiratory depression and preventing death and other serious outcomes.

Several pieces of information can help support the effectiveness of NNS in the hands of consumers when we consider a switch to nonprescription status. If a DFL is used that demonstrates comprehension among a diverse population and the HFVS demonstrates that representative consumers can use the product properly, then this would suggest that the product will be efficacious in the hands of consumers without the help of a learned intermediary.

As mentioned above and as previously communicated in a 2019 Federal Register notice (84 FR 8728), FDA has taken the unprecedented step of designing and assessing comprehension of two versions of a model naloxone DFL for use by industry to support a nonprescription drug application.[9, 10] As such, the Applicant was able to use this model DFL without changes to the previously tested portions to avoid performing a comprehensive LCS for the portions previously tested. For the purposes of this AC meeting, we have included information on the model DFL and the study validating its use (CONFER Pivotal Label Comprehension Study)[11] in Section 8 of this briefing document, as findings from the study may be helpful to AC members in understanding the underpinnings for the Applicant's development program. However, since FDA has already concluded that the tested portions of the model DFL are acceptable for use in the nonprescription setting, we are not asking the AC to discuss the conduct or results of this study.

The Applicant conducted a simulated-use HFVS to assess the ability of consumers to correctly follow the product-specific instructions for use in the DFL. The results of this study are presented in Sections 5 and 8.14 of this briefing document. We ask the AC to discuss the results of this study and its implications for product labeling, taking into account potential study design limitations.

Finally, we draw attention to the overall packaging and labeling of NNS, other than the DFL and ask the AC to consider the following issues. Would the inclusion of a package insert containing the DFL

[9] https://www.fda.gov/media/119743/download
[10] https://www.fda.gov/media/119744/download
[11] https://www.fda.gov/media/119745/download

instructions for use be beneficial to include in the blister package of each device? Might it be possible that some consumers may not choose to keep the entire NNS box, and instead just carry the NNS device in its blister packaging? If this were to occur, consumers may not have necessary directions for use in the case of an emergency.

3.2 Safety of Naloxone as a Prescription Product

The safety of NNS is based on NDA 016636 as a prescription for injection 0.4 mg/1 mL and on NDA 208411 as the prescription NNS 4 mg. The safety associated with these products comes almost exclusively from postmarketing safety databases and the literature. According to the prescription label for naloxone for injection:

- The following AEs were identified primarily during postapproval use of naloxone HCl in the postoperative setting: 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 HCl in postoperative patients have resulted in significant reversal of analgesia, and have caused agitation. 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.
- 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, and 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.

Additionally, the label for NNS notes that the most common adverse reactions seen in 30 healthy adults in a PK study were increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, rhinalgia, and xeroderma.

Accordingly, the key safety issues that were the focus of FDA's analysis of postmarketing safety databases as part of our review of this application included the following:

- Naloxone-induced precipitated withdrawal.
- Limited efficacy.
- Device use errors and medication errors.

3.3 Safety Considerations for a Switch

The safety of naloxone relies on over 50 years of prescription postmarketing data for naloxone in injectable formulations and 6 years of postmarketing data for prescription NNS use on the market. It is also supported by limited clinical trial data generated during drug development of both the injectable and nasal spray products. NNS is primarily marketed in the United States and Canada, although other naloxone products are used worldwide in different dosage forms and conditions of use. The primary value of FDA reviewing postmarketing safety data and literature is to identify unexpected or serious events not previously recognized for a product and, to the extent possible, evaluate known AEs specific to the proposed product that might represent issues that would affect labeling for consumers.

Safety of the nonprescription NNS is further supported by studies that evaluate comprehension of the label with the LCS (Section 4). In addition, the nonprescription NNS is supported by the HFVS (Section 5) which evaluates whether the user interface can be used safely and effectively.

3.3.1 Sources of Postmarket Safety Data

For this NDA, the Applicant provided an analysis of domestic and foreign postmarketing safety data for intranasal naloxone with special attention to potential safety issues that may arise during nonprescription NNS use. Data sources included the Applicant's pharmacovigilance database (ARGUS), FDA Adverse Event Reporting System (FAERS), and World Health Organization's Vigibase (see Section 8.13 for full database descriptions). The Applicant conducted a literature search using EMBASE to look for U.S. reports of AE cases.

FDA also conducted an independent evaluation of FAERS, Embase, and PubMed for naloxone-related AEs (all routes of administration and a subset analysis for IN naloxone) between January 1, 2016 and November 17, 2022. Attention was directed to safety topics of interest including naloxone-induced precipitated withdrawal, limited efficacy, and device use errors/medication errors.

It should be noted that limitations exist for all AE databases. There may not be a causal relationship between events reported and the product. Many of the case reports are not available or lack sufficient detail and preclude a full evaluation. Additionally, there may be significant underreporting. As many factors can influence whether or not an event is reported, the databases cannot be used to calculate the incidence of an AE in the U.S. population.

Though not a source of safety data, FDA also evaluated U.S. drug utilization and distribution patterns for naloxone products (all routes of administration) using proprietary databases available to FDA (see Section 8.13 for full database descriptions). Distribution and utilization data provides context on the availability of naloxone and estimate of potential patient exposure to naloxone. The IQVIA National Sales Perspective™ (NSP) database was used to obtain the annual estimated number of naloxone units (vials, prefilled syringes, autoinjectors, and nasal sprays) sold from manufacturers to various channels of distribution in the United States from 2017 to 2021. We used this data source to determine sales to all settings[12] that are captured in IQVIA NSP. We used the Symphony Health Metys™ database to obtain the annual estimated number of naloxone prescriptions dispensed from U.S. outpatient retail, mail-order, and long-term care pharmacies, stratified by product formulation, from 2017 to 2021.

3.3.2 Safety Summary

FDA's review of the Applicant's assessment of postmarketing safety data from ARGUS database as well as their presentation of data from the FAERS and World Health Organization databases revealed no new safety signals of concern and the findings were consistent with the prescription labeling for the product. For brevity, only the data from ARGUS is summarized in this briefing document (Section 3.3.3).

FDA conducted an independent review of the FAERS data that looked closely at selected safety areas of concern that included naloxone-induced precipitated withdrawal, limited efficacy, and device use errors/medication errors. FDA's review (Section 3.3.5) revealed no new safety signals of concern,

[12] The NSP™ database does not capture distribution of drugs outside of the typical pharmaceutical distribution supply chain, such as donations or direct sales from manufacturers. Also, the analyses provided in this review may not provide any visibility into distribution to harm reduction programs and the settings impacted by them.

although it did yield some observations that could inform the labeling and product design for nonprescription NNS.

3.3.3 ARGUS

The Applicant notes that in the period from (b) (4) to (b) (4), there was a cumulative distribution of (b) (4) unit cartons of NNS in the United States and (b) (4) unit cartons distributed elsewhere ((b) (4)). Each carton contains two, 4 mg Narcan nasal sprayers; which results in a total of (b) (4) units of NNS distributed over the covered period.

The Applicant notes that its ARGUS database contains cases presumed to be related to the use of INN and not that delivered by other routes of administration. The Applicant notes that cases received or identified under the trade name Narcan are entered in the database as such; if not, they are entered into the database under the generic name "naloxone." Of the 397 unique cases reported, 300 cases mentioned NNS and 97 did not mention NNS (Table 2). Serious outcomes are defined as having any adverse drug event that results in death, a life-threatening event, hospitalization, disability or permanent damage, congenital anomaly or birth defect, requirement of an intervention to prevent permanent impairment or damage, or other serious important medical events. A total of 93 serious cases (23.4%) were noted over 5.5 years.

Table 2. Summary of ARGUS Serious Case Reports

Case Reports	Total, n (%)	Naloxone, n (%)	NNS, n (%)
Serious	93 (23.4)	39 (40.2)	54 (18)
Nonserious	304 (76.6)	58 (59.8)	246 (82)
Total number of cases	397 (100)	97 (100)	300 (100)

Source: Module 5.3.5.3 Emergent (ARGUS) Safety Database Analysis, submitted November 22, 2022, Table 1, p. 4.
Abbreviations: n, number of subjects with case reports; NNS, Narcan Nasal Spray

Evaluating serious cases by age, no serious case (0%) occurred in a child of age <2 years, 5 cases (5.4%) occurred in children ages 2 to <18 years, 58 cases (62.4%) occurred in adults ages 18 to <65 years, 5 cases (5.4%) occurred in adults ages ≥65 years, and in 25 cases (26.9%) age was unknown. Table 3 shows the most frequently reported preferred terms occurring at a >1% rate among serious cases.

Table 3. Most Frequently Reported Preferred Terms (>1%) Among Serious Cases—ARGUS

Preferred Term	<2 Years n=0	2-<18 Years n=23	18-<65 Years n=206	≥65 Years n=56	Unknown n=47	Total N=332 n (%)
Death	0	0	5	0	9	14 (4.2)
Drug withdrawal syndrome	0	0	12	0	0	12 (3.6)
Seizure	0	1	9	0	2	12 (3.6)
Drug ineffective	0	0	6	0	3	9 (2.7)
Loss of consciousness	0	0	6	1	0	7 (2.1)
Toxicity to various agents	0	2	3	0	1	6 (1.8)
Vomiting	0	0	5	0	1	6 (1.8)
Drug dependence	0	0	5	0	0	5 (1.5)
Overdose	0	0	3	2	0	5 (1.5)
Cardiac arrest	0	1	3	0	1	5 (1.5)
Unresponsive to stimuli	0	0	3	2	0	5 (1.5)
Respiratory failure	0	1	1	0	2	4 (1.2)
Unintentional use for unapproved indication	0	0	2	1	1	4 (1.2)

Source: Module 5.3.5.3 Emergent (ARGUS) Safety Database Analysis, submitted November 22, 2022, Appendix I, p. 16.
Abbreviations: ARGUS, Applicant's pharmacovigilance database; N, number of subjects; n, number of subjects with reported preferred term

The Applicant provided FDA with case summaries limited to those reporting serious outcomes. In reviewing the case summaries involving a fatal outcome (26/397; 6.5%), the majority of the cases contained too little information to show an association between naloxone and the fatal outcome. Many cases showed toxicity to multiple agents besides opioids and two cases reported the victim had been given naloxone too late. Five serious cases were assessed in children <18 years—four reported use of naloxone in an overdose occurring with a nonopioid agent, including two deaths, which appeared to be due to the underlying nonopioid drug of overdose rather than naloxone use. In the remaining serious pediatric case, a 17-year-old experienced seizure and ministrokes in the setting of naloxone use for opioid overdose. Geriatric cases were also assessed. Although there were 21 case reports in those ≥65 years of age, only five were serious and none was fatal. The most frequently occurring AE among serious geriatric cases often did not appear to be directly related to naloxone use and no AE appeared disproportionately in this population. Four case summaries in pregnant women were reviewed; only one had a serious outcome of a premature delivery, but this case was confounded by the use of multiple psychoactive medications and nicotine. Drug allergy and hypersensitivity was assessed; three (3/397; 0.8%) serious cases were identified. None was fatal; one reported anaphylactic shock but recovered and two other cases had too little detail to confirm the condition was related to naloxone. Discussion of naloxone-induced precipitated withdrawal, limited efficacy, and device use errors/medication errors are deferred to FDA's evaluation of the FAERS database.

In summary, serious case summaries were provided for review; these cases were often confounded or lacked adequate detail. Although it is acknowledged that there are inherent limitations of postmarketing safety analysis, given the low volume of cases reporting fatal or serious outcomes and the more than 29 million units of NNS distributed in the last 5.5 years per the Applicant, these data do not suggest any significant or new safety concerns associated with use of the product.

3.3.4 Drug Distribution and Utilization

FDA conducted an independent analysis of distribution and utilization. From 2017 to 2021, manufacturer sales and dispensed prescriptions of all naloxone formulations increased dramatically.

Manufacturers distributed 5.1 million units of naloxone in 2017, which increased by 81% to nearly 9.3 million units by 2021. These increases were largely driven by increases in nasal spray formulations, which increased from 1.1 million units in 2017 to 5.6 million units in 2021.[13]

There was a similar shift towards nasal spray in the dispensed prescription analysis. Table 4 summarizes the nationally estimated number of prescriptions for naloxone products dispensed from U.S. outpatient retail, mail-order, and long-term care pharmacies, stratified by product formulation, annually from 2017 through 2021. The number of naloxone prescriptions dispensed increased from approximately 359,000 prescriptions in 2017 to 1.5 million prescriptions in 2021, mainly due to an increase in the nasal formulation. The proportion of nasal formulations dispensed among the total naloxone prescriptions increased from 67% in 2017 to 97% in 2021, while the proportion of injectable naloxone dispensed decreased from 33% to 3.5% during the same study period.

Table 4. Nationally Estimated Number of Naloxone Prescriptions Dispensed From U.S. Retail and Mail-Order Pharmacies, Stratified by Formulation, Annually 2017 to 2021

Product	2017 N (%)	2018 N (%)	2019 N (%)	2020 N (%)	2021 N (%)
Nasal	240,190 (66.9%)	630,484 (86.9%)	1,083,858 (94.3%)	1,202,586 (96.5%)	1,453,356 (96.5%)
Injectable	118,845 (33.1%)	95,319 (13.1%)	64.915 (5.7%)	44,240 (3.5%)	51,960 (3.5%)
Total	359,035 (100%)	725,803 (100%)	1,148,773 (100%)	1,246,826 (100%)	1,505,316 (100%)

Source: Symphony Health Metys™.
Time period 2017 to 2021. Data extracted in January 2022. These data do not include naloxone products that individuals received outside of a pharmacy setting, such as from organizations like harm reduction programs.
Abbreviation: N, number of subjects with the indicated product

It is noted that naloxone products are distributed not only using the traditional pharmacy supply chain, such as hospitals, clinics, retail outlets, mail-order pharmacies, health maintenance organizations, home health care, universities, and government facilities. Naloxone is also distributed outside the typical health care supply chain to reach those without health insurance, those who are using illicit substances who may be reluctant to seek medical care, and family and friends of opioid users. These distribution channels may include products donated or sold directly to groups such as HR programs, prisons, and other entities. These units distributed outside the traditional wholesale pharmaceutical distribution supply chain are not captured in estimates obtained from proprietary databases available to FDA. The dispensed prescription analysis included data from U.S. outpatient retail, mail-order, and long-term care pharmacies only. In the outpatient setting, individuals receive naloxone from other health care settings that are not captured in this analysis.

3.3.5 FDA's Analysis of FAERS and Safety Topics of Interest

FDA conducted an independent FAERS search from January 1, 2016 (the year of the marketing launch of NNS) to November 17, 2022 for cases involving naloxone, especially INN use in a community setting. The Medical Dictionary for Regulatory Activities version 25.1 was used.

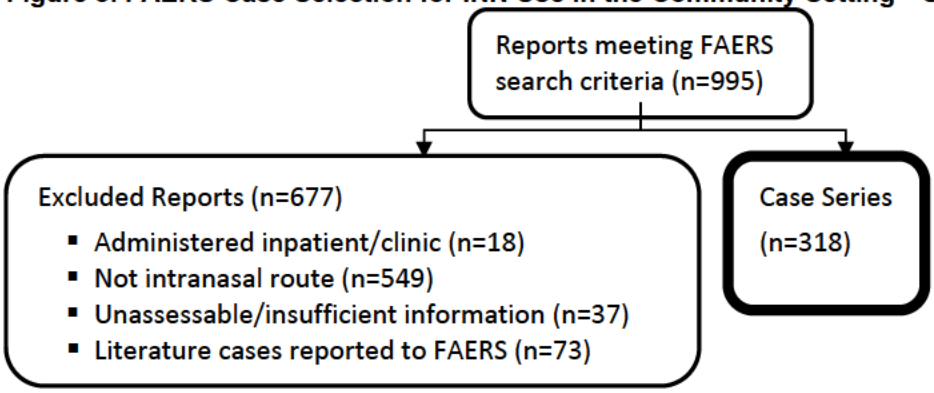
The search initially included all U.S. case reports of naloxone as a single ingredient and excluded duplicates, non-U.S. reports, and cases where it was unclear if naloxone was a single reversal agent used. This search yielded 995 cases reporting naloxone use from all routes of administration. Cases were

[13] IQVIA NSP Time period 2017 to 2021. Data extracted July 2022.

then screened for use in the community setting and those cases where naloxone was administered in an inpatient or outpatient clinic setting were excluded. Cases were also excluded if the route of naloxone administration was unknown and if the dose administered was not IN. Additionally, case reports that were unassessable or had insufficient information were excluded.

The case selection criteria for FAERS cases reporting the use of INN in the community setting are shown in Figure 3; a total of 318 cases were included.

Figure 3. FAERS Case Selection for INN Use in the Community Setting—Subset Analysis



Source: FDA review of FAERS data.
Abbreviations: FAERS, FDA Adverse Event Reporting System; INN, internasal naloxone; n, number of subjects

Of the 318 FAERS cases selected, 0.3% were age <18 years, 13.8% were ages 18 to <40 years, 11.3% were ages 40 to <65 years, and 3.8 % were ≥65 years of age. A total of 70.8% did not report an age. Males constituted 47.8% and females 38.4% with the remainder unreported. A total of 79.2% of cases reported the reason for INN use was for the emergency treatment of known or suspected opioid overdose, 18.2% reported accidental use, and 2.5% reported a nonindicated condition. Cases were assessed for number of doses administered and most reported the use of only one or two doses, that is, up to 8 mg, the amount contained in one carton of NNS.

In analyzing the cases, those administering the naloxone were defined as either the general public (untrained laypeople), trained laypeople, or HCPs (Table 5). When information was available, the individual administering the naloxone was a layperson (general public) 49.4% of the time, a trained layperson 8.5% of the time, and a health care professional 4.1% of the time.

Table 5. Definitions of Individuals Responding to OA-OHCA Based on Training

	Definition	Likely educational setting/resources
General public	Untrained lay public	Public service announcements; Stand-alone OEND kits; Virtual/online courses; EMS dispatcher instructions
Trained laypeople	Non-health care personnel with formal training • Naloxone dosing • Basic life support • Other skills	OEND programs; Occupational first-aid programs; Instructional (certification) courses for people likely to encounter overdose
Health care providers	Existing health care professionals with resuscitation capabilities	Formal health care training; resuscitation training; ongoing quality improvement and simulation
EMS = emergency medical services OA-OHCA = opioid-associated out-of-hospital cardiac arrest OEND = overdose education and naloxone distribution		

Source: Modified from Dezfulian et al. (2021).

3.3.5.1 Naloxone-Induced Precipitated Withdrawal

In order to assess opiate withdrawal in the cases selected, the Clinical Opiate Withdrawal Scale (COWS) (Section 8.12) was used to evaluate cases of reported naloxone-induced precipitated withdrawal. COWS is a tool for clinicians to diagnose and manage opioid withdrawal (Wesson and Ling 2003). It was developed in the late 1990s, initially as a guide for buprenorphine treatment. It is most frequently used for differentiating the presence versus absence of withdrawal as well as identifying clinically significant withdrawal. Since the early 2000s, it has become more widely used as a clinical tool due to ease of administration and consistency between evaluators. The utilization of the COWS scoring tool within the case series was not how the COWS tool is intended to be used (i.e., at the bedside), but it provided an objective way to report withdrawal symptoms, which are by their nature, subjective.

The case definition for naloxone-induced precipitated withdrawal was made by reviewing cases where opioid withdrawal occurred after naloxone administration as reported either by a HCP or by a layperson and supported by case details provided in the report (e.g., specific signs and symptoms associated with the COWS). COWS scores were calculated to support the determination of opioid withdrawal and, if possible, quantify severity. COWS is an 11-item scale (total score range 0 to 45) that provides a reproducible assessment of signs and symptoms of opioid withdrawal. The score comprises 11 items: resting pulse, sweating, gastrointestinal upset, tremor, restlessness, yawning, pupil size, anxiety or irritability, bone or joint aches, gooseflesh skin, runny nose or tearing (Wesson and Ling 2003). If the reports did not include these specific elements, they were assumed not to be present. Therefore, the derived COWS scores represented the minimal score and may have, in actuality, been higher.

Cases reported in FAERS support the known AE of naloxone-induced precipitated withdrawal, which is included in the prescription NNS labeling under Section 5, Warnings and Precautions. As a pure competitive opioid receptor antagonist, naloxone reverses all receptor-mediated opioid actions including central nervous system and respiratory depression due to opioids. Naloxone administration to individuals with exposure-related opioid receptor neuroadaptations may precipitate withdrawal from a resultant catecholamine increase (Connors and Hamilton 2019).

A total of 180 cases (180/318, 56.6%) were identified reporting withdrawal or symptoms consistent with withdrawal. No deaths were reported and 35 withdrawal cases (35/180, 19.4%) reported a serious outcome. Gastrointestinal upset, anxiety/irritability, and sweating were the most commonly scored items on the COWS scale. Overall, there were few cases with a COWS score ≥5. Per the COWS scale, scores of 5 to 12 indicate mild withdrawal. Other more severe non-COWS withdrawal symptoms such as

pulmonary edema (n=2) and seizures (n=8) were also reported to FAERS. Pulmonary edema and seizures are already included in the NNS labeling under Section 5, Warnings and Precautions, and described as a potential consequence of abrupt postoperative withdrawal. The hypothesized mechanism for pulmonary edema 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"[14].

3.3.5.2 Limited Efficacy

Multiple factors contribute to the effectiveness of INN including the severity of the overdose, if other substances are involved, if the user did not have enough naloxone, if time elapsed between when the overdose occurred and when naloxone is administered, and the administration technique. Naloxone needs to be administered as quickly as possible after overdose to prevent death.

The 318 cases describing INN use in the community setting were evaluated for mentions of adverse events associated with limited efficacy. A total of 24 cases (24/318, 7.5%) were identified in the analysis of limited efficacy. Serious outcomes occurred in 14 cases (14/24, 58.3%), with two deaths. The analysis of limited efficacy cases was challenging as cases often provided limited information precluding a meaningful assessment. Information about the time elapsed between when the overdose occurred and when naloxone was administered was often unreported. Additionally, 75% of cases did not report the specific opioid intended to be reversed (e.g., partial agonists) or if other substances were involved in the overdose, both of which could affect the efficacy of naloxone. Thus, it was not possible to fully ascertain causality of limited efficacy in most cases.

3.3.5.3 Device Use Errors and Additional Medication Errors

A separate FAERS search was conducted for device use errors and medication errors for prescription NNS and Kloxxado Nasal Spray. The National Coordinating Council for Medication Error Reporting and Prevention Taxonomy of Medication Errors [15] was used to describe the medication error and contributing factors. Cases that were excluded included: scenarios of naloxone hydrochloride nasal spray device malfunction, cases where insufficient information was provided to determine whether a user error occurred or device malfunctioned, cases describing use of naloxone injection and not the naloxone nasal spray, cases of administration of an expired product, cases where an unclear dosage form of naloxone was used, and a case of medication error involving another product that was not naloxone nasal spray.

A total of 71 medication error cases were identified for further analysis and are discussed below.

Device Use Errors

A total of nine cases involving device use error for prescription INN were identified in the FAERS search; all cases involved NNS. All nine cases were reported as nonserious, and five of these nine cases did not report a contributing factor to the error. The cases described wrong administration technique related to device use errors, including:

- Not waiting 2 to 3 minutes between doses (n=3).
- Spraying medication into the air instead of patient's nostril and thus, wasting a dose (n=3).

[14] See Narcan NS at https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/724df050-5332-4d0a-9a5f-17bf08a547e1/spl-doc?hl=Narcan

[15] https://www.nccmerp.org/taxonomy-medication-errors-now-available

- General confusion about the use of the device (n=2).
- Administering repeated doses of medication to the same nostril (n=1).

In six of the cases, the narratives indicated that the use of naloxone nasal spray occurred during the emergency situation when the person was not breathing or appeared not to breathe. These six cases reported the user not waiting 2 to 3 minutes between two doses (n=3), spraying the nasal spray into the air (n=2), or administering repeat doses of the product to the same nostril (n=1). Of these six cases, five reported that users were either a friend or a family member of the affected patient, and the remaining case reported the device user was a police officer. One of the six cases specifically reported that the user panicked. However, the remaining five cases did not cite root cause or contributing factor information. In all six cases that reported an emergency situation, patients recovered. None of the six emergency situation cases reported whether Instructions for Use/QSG/carton labeling with the use instructions were referred to during the use of the product or whether the user read the Instructions for Use/QSG at any time prior to using the product.

Three of the nine cases involved nonemergency use of the product. The narratives for these three cases suggested that the users were trying to train themselves on how to use the device in case of an emergency (n=3). One case reported the user was not sure how to work the device and nothing came out (n=1); in the second case, the user stated they were confused how to use the device and continued pressing the plunger and nothing came out (n=1); and the third case described a user who was confused and sprayed the product into the air and hence wasted a dose (n=1). In two of these cases, the case narrative did not state whether the person referred to the Instructions for Use/QSG/carton labeling with instructions. In the remaining case, the user was referring to the Instructions for Use, but still was confused about taking off a cap and pressing the red plunger. The user in the case reported that the instructions made it sound like one just needs to open and spray in nostril and they questioned if there were additional steps in between. We note that neither naloxone nasal spray device (i.e., Narcan or Kloxxado) has a “cap” nor did it have a cap previously at the time of the approval. Thus, it is unclear which Instructions for Use/device the user was referring to and why the user was confused.

Although some device use errors occurred, they reported nonserious outcomes. Additionally, with the exception of one case, the remaining cases were unclear with regards to whether the user referred to the approved prescription labels and labeling during use of the product.

In terms of a safety assessment related to the device use error, if a user chooses to test the device and thereby sprays medication into the air, this will waste a dose. If that is the only device/dose available at the time, a person would not get an emergency treatment for the opioid overdose, which can potentially lead to death. Additional device use errors such as not waiting two to three minutes between doses and using the product in the same nostril also occurred. These latter device use errors represent a deviation from labeled dosing and use, which could have an impact on efficacy. However, missed dose appears to be a more significant safety risk from the device use error perspective. As such, postmarket data appear to support packaging of two devices together in one carton as a single sales unit to minimize the likelihood that a dose is not available when needed.

Additional Medication Errors

FDA identified additional medication errors that may help inform the considerations for labels and labeling for the nonprescription INN:

- Wrong Indication (n=58).
- Accidental wrong storage error (n=4).

Wrong Indication

The wrong indication cases reported patients or caregivers mistakenly administering INN due to lack of knowledge regarding what naloxone is used for and thinking it is used for indications other than stated in the package insert labeling (e.g., sinus issues, allergy, asthma, diabetes) or thinking it is another product (i.e., inhaled morphine, Flonase, Imitrex, or substitute for Percocet). In some cases, patients administered INN without knowing what the product was for, but since it looked like a nasal spray they assumed they were prescribed it for one of their conditions. One case specifically stated that the prescription label was wrapped all around the carton and they could not understand what the product was for. Other cases did not report whether patients attempted to read and comprehend what INN was indicated for. However, several cases reported that patients saw "nasal spray" on the box. One case reported administration of Narcan instead of Imitrex. It is noted that there is a currently marketed Imitrex product that uses the same nasal device configuration as prescription Narcan; thus, the similarity between Imitrex inhaler device and Narcan device appears to be a contributing factor for confusion.

Of the 58 cases that reported use for the wrong indication, 3 cases reported a serious outcome, including one death. Of the three cases reporting a serious outcome: one fatal case reported that the patient used INN thinking it would "help her sinus issues." The patient had multiple comorbidities (chronic pain, "abnormal blood pressure", "sinus issues") and used multiple medications (furosemide, tramadol, clonazepam, NicoDerm, and Cymbalta) for her health conditions. Additionally, the date of the patient's death relative to naloxone use was not reported. As such, it is difficult to assess whether INN is related to the patient's death. The two other serious cases reported "Other" serious outcomes. Both reported withdrawal symptoms (COWS scores of 4 and 5), after patients accidentally used INN while thinking it was an allergy spray and to relieve congestion respectively.

Although prescription INN products state the indication on the carton labeling and instructions for use, it is unclear whether patients read the carton labeling. Additionally, given that the product is prescribed by a doctor and filled by the pharmacy, patients may not realize why they are prescribed this medication. For the nonprescription product, patients or caregivers will have to select the product for the suspected or known opioid overdose off the shelf, thereby knowing why they are purchasing the medication. Additionally, the LCS conducted for the model DFL addressed that general consumers were able to understand that the product's use is "to revive someone during an overdose from many prescription pain medications or street drugs such as heroin." Despite these mitigating factors, we recommend the name and the indication of the product be prominently stated on the labels and labeling to ensure lay users are able to see the information.

Accidental Wrong Storage

Four cases were identified related to accidental wrong storage of the product in freezing temperatures or temperatures over 104°F, outside the recommended temperature range for storage. In all four cases, patients were aware of the correct storage temperature, but accidentally stored the product incorrectly. In some cases the product was stored in a car that reached freezing temperature or temperatures over 104°F. In all of these nonserious case reports, none of the potential users of the naloxone administered the product. As such, given that potential users were aware of the correct storage temperature, and yet whomever stored the product left the product accidentally under the wrong storage conditions, it may be useful to consider whether increasing the prominence of storage information might be helpful.

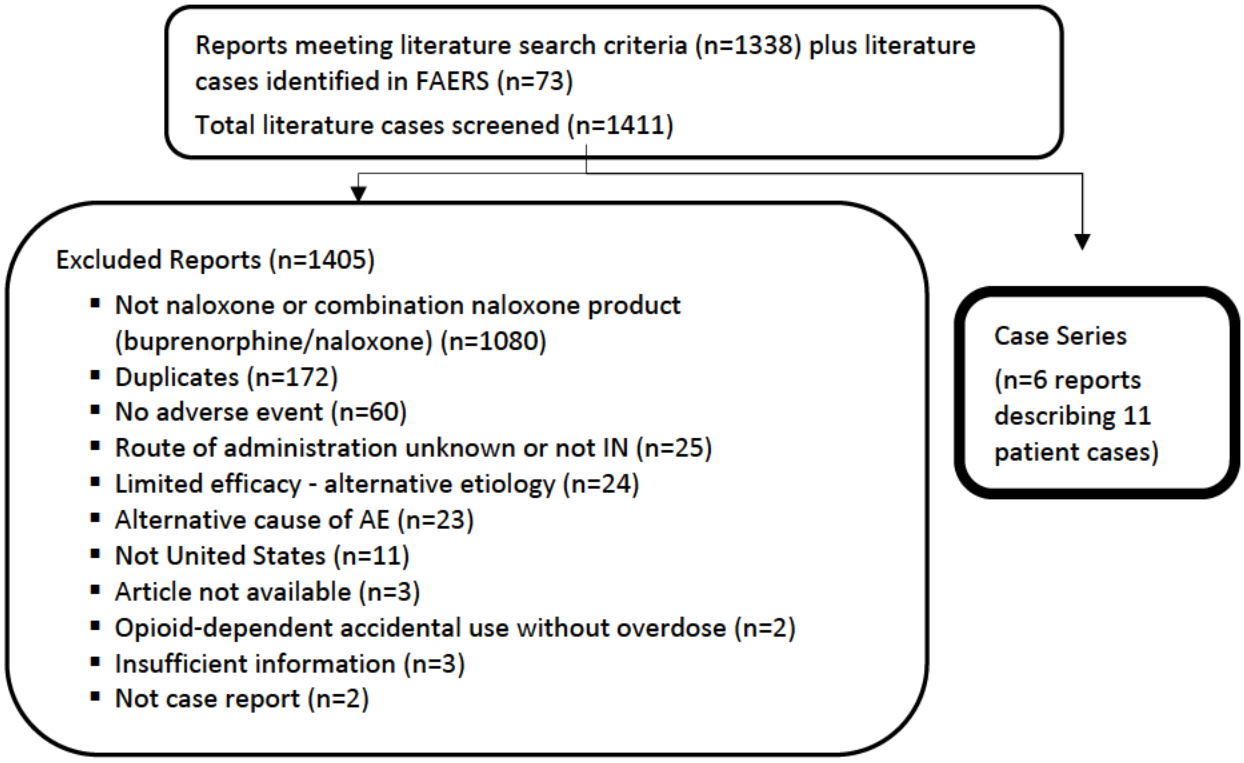
3.3.5.4 *Deaths*

Case reports for deaths were few and were not informative with regard to time elapsed between INN administration and the individual's death, the confirmed substance that the individual had overdosed on, or autopsy information.

3.3.6 Literature Review

The literature was reviewed from 2016 to 2022 by both the Applicant and FDA using Embase as well as PubMed. This section covers FDA's review which focused on cases and case series published that described use of INN with safety outcomes, as well as reviews that summarized issues related to use of INN in the community. Specifically, for the case reports reviewed by FDA, the same case selection criteria were applied to literature cases of INN as were applied to the review of FAERS reports as described in Figure 4.

Figure 4. Literature Case Selection for Intranasal Naloxone (INN) Analysis



Source: FDA literature review.
Abbreviations: AE, adverse event; FAERS, FDA Adverse Event Reporting System; IN, intranasal; n, number of subjects

After applying the exclusion criteria, the literature case series included six reports describing 11 patients who experienced either an AE or device use error associated with INN use. These include seven patients who experienced pulmonary edema (Veet et al. 2017; Yarlagadda et al. 2020; Kummer et al. 2022). All cases of pulmonary edema required hospitalization and in some cases, intubation, but all resolved rapidly. Pulmonary edema is a known potential AE associated with naloxone and included in the prescription labeling in Section 5, Warnings and Precautions, where it is described as a potential

consequence of abrupt postoperative withdrawal.[16] Additionally, two cases described limited efficacy, requiring a higher-than-typical dose, possibly related to a superpotent opioid, and two cases described naloxone-induced precipitated withdrawal, one of whom had rapid administration of multiple doses (five additional doses in rapid succession) resulting in overexposure and prolonged naloxone-induced precipitated withdrawal. The other case, who had a COWS score of 12, was mitigated by administration of buprenorphine by emergency medical services (Brenner et al. 2021; Carroll et al. 2021). These cases show the importance of calling 911 in addition to giving naloxone.

For the two cases of limited efficacy in which higher doses of naloxone were required, they were in two overdose victims with a history of heroin use who most likely also had carfentanil intoxication (Bardsley 2019), a very-high-potency opioid. These cases are instructive that if high-potency opioids are suspected, then repeat dosing with higher doses of naloxone may be required. This is captured in both the naloxone prescription labeling and in the proposed nonprescription DFL for naloxone. The prescription labeling states, "the requirement for repeat doses of NARCAN Nasal Spray depends upon the amount, type, and route of administration of the opioid being antagonized" and the DFL captures this concept by advising that a dose of naloxone should be administered, call 911, and then if the person does not wake up, continue to give doses every 2 to 3 minutes until the person wakes up. Complicating this general advice is the possibility of an alternative unrecognized cause of somnolence that would not respond to opioid antagonism that might be the cause of failure to arouse. This underscores the importance of rapidly activating emergency medical services for further evaluation and management.

Pertaining to naloxone-induced precipitated withdrawal, one case described a patient who was given six doses of naloxone in rapid succession by an untrained bystander; the recipient experienced severe and prolonged agitation (Brenner et al. 2021). Another had an initial COWS score of 12 after receiving one dose of INN, but this was mitigated by receiving a dose of buprenorphine from emergency medical services, which reduced her COWS score to 4 (Carroll et al. 2021). This may highlight a need to educate consumers about the symptoms of naloxone-induced precipitated withdrawal, which is captured in the DFL as a warning to expect symptoms such as shaking, sweating, nausea, or feeling angry as well as reinforcing the need to "Call 911."

In addition to reviewing case reports, FDA conducted an additional search of the published literature to evaluate approved INN products (4 mg and 8 mg products) and response rate to treatment in the setting of a changing opioid epidemic that includes increasing exposures to superpotent opioids such as fentanyl and its analogs. Using the PubMed database and limiting the search to 2016 to 2022, the search identified very few articles specifically addressing approved INN products. Many articles covered naloxone use from all routes of administration, including off-label use of naloxone with mucosal atomizer devices. These articles often discussed multiple naloxone administrations of various doses, formulations, and routes equivalently. Two articles specifically addressed approved INN products.

A 2018 article (Avetian et al. 2018) was sponsored by Adapt Pharma, Inc. and described a survey of first-responder or community-based organizations located across the United States that were known to have received and distributed 4 mg NNS in their communities. Eight organizations reported a total of 261 attempted opioid overdose reversals using NNS between April and August 2016. When information on the presumed drug of overdose was provided, 5.2% of cases were presumed to involve fentanyl. When information on numbers of NNS doses was known (254 cases), the vast majority, 97.6% (248/254) required only one or two doses, and the remaining 2% (5/254) required three doses, and 0.4% (1/254) required four doses. The survival outcome after NNS administration was reported for 245 cases; 98.8%

[16] See Narcan NS at https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/724df050-5332-4d0a-9a5f-17bf08a547e1/spl-doc?hl=Narcan

(242/245) were reported as successful. Of the three deaths reported, NNS was reportedly administered too late in two individuals and details were not provided for the third case. This suggests that at present, providing two doses in a carton appears on target when surveying several community-based organizations.

A more recent article (Abdelal et al. 2022) was sponsored by Hikma Pharmaceuticals and described a survey of U.S. residents who reported both witnessing an overdose and administering 4 mg NNS in the past 12 months. Participants were required to reside in regions of the United States known to have high levels of fentanyl use. A total of 125 participants were recruited between February 2021 to March 2021. Thirty percent of cases were presumed to involve fentanyl. Survey respondents reported that 70.4% of cases involved one or two doses of NNS, 13% involved three doses, and 17% involved four or more doses. Ninety-five percent of cases were successfully revived (88% or 110/125 of cases were revived at the scene and 7% or 9/125 were revived later) and 5% (6/125) of cases were not revived. This more recent study, where the survey was undertaken in an area known to have high levels of fentanyl use, suggests that there appears to be increasing need for redosing among those who have used high potency opioids. These two articles, while acknowledged to be sponsored by industry, provide relevant information about NNS performance in the community setting and demonstrate reasonably high reversal rates as an overall outcome.

3.3.7 Pediatric Safety Considerations

Establishing efficacy in the pediatric population using PK data was not required for children for approval of NNS. At the time of approval, there were concerns that IN drug absorption in children could be adversely affected by a poorly fitted actuator tip and differences in the nasal morphology, nasal cavity dimensions, and pattern of IN particle deposition between adults and children. However, review of postmarketing safety reports received since the approval of NNS show no evidence suggesting drug failure or other safety concerns specific for children.

One other consideration is whether young users of NNS can effectively administer the product. Young children may potentially be the first and only responder in a household if a medical crisis occurs. Approximately 12.3% of U.S. children under 17 years of age live with at least one family member with a substance use disorder. Teaching these children how to administer naloxone correctly could be life-saving—particularly for families consisting of single parents or in families where a school-aged child is left at home with an older sibling and/or their friends who use opioids. FDA validated comprehension of the naloxone model DFL down to 15 years of age. The HFVS simulation only assessed performance of a rescue down to age 15 years. This constitutes a gap in our understanding of how a younger user group would perform.

4 Label Comprehension Study

4.1 Label Comprehension Overview

LCS are conducted for virtually all new prescription to nonprescription switch NDAs. These studies should be designed and conducted based on the corresponding FDA Guidance for Industry. Label comprehension is foundational in a nonprescription drug development program, to determine if the DFL and the consumer information leaflet (if applicable) successfully communicate important information about a drug to ultimately facilitate the safe use of the drug.

In an LCS, applicants need to identify the most important communication objectives that need to be assessed as primary objectives. These are the most important concepts, from the viewpoint of safety

and efficacy, that need to be understood by consumers. Target thresholds are established a priori, and are based on clinical implications if consumers fail to adequately understand the labeled items. For instance, for a hypothetical nonprescription product, a target threshold for comprehension of "do not use if you have liver disease" could be established at 90%, because there would be serious medical consequences for the consumer with liver disease if the consumer were to use the product.

Adequate comprehension is assessed by comparing the established threshold with the lower bound of the two-sided exact 95% confidence interval for the comprehension rate. For example, if the lower bound of the confidence interval is 92% and the target threshold is 90%, adequate comprehension would be demonstrated. The lower bound is utilized because it accounts for the uncertainty in the estimate of the comprehension rate. It is important to note that in nonprescription consumer behavior studies, success thresholds are targets—and not automatic "hard stops." If an objective fails to meet a threshold, the clinical impact is considered within the total risk-benefit assessment.

FDA typically asks applicants to include approximately one-third LL representation in their consumer studies, reflecting estimated proportions in the population based on the 2003 National Adult Assessment of Literacy. Generally, participants in consumer studies are administered the Rapid Estimate of Adult Literacy in Medicine test, which is a validated literary assessment tool. For the purposes of nonprescription regulatory consumer studies, LL is defined as scoring <60 on the Rapid Estimate of Adult Literacy in Medicine test, which represents a reading level of eighth grade or below.

Secondary communication objectives are intended to address areas less critical to safe and appropriate use, yet clinically relevant. Secondary communication objectives typically are not assessed against target thresholds.

LCSs usually enroll as demographically diverse a population as possible. Generally, the studies include 300 to 600 subjects from a variety of testing sites across the United States. Typically, LCSs are conducted with "all comers"; they are usually intentionally not limited to sufferers of a condition, because anyone should be able to pick up a DFL and/or a consumer information leaflet and understand what it says. Also, anyone can develop a need for a product in a therapeutic category that is new to them, or alternatively, be in a position to administer a medication on behalf of an opioid user for a condition that the administrator does not know much about.

In an LCS, consumers are given the DFL to read at their own pace. They are then asked questions about the label, and can refer back to it as much as they want. It is not a test of memory, but rather an "open book" test to assess whether consumers are aware of and can understand key elements presented in the DFL. Questionnaires need to be constructed targeting the communication objectives in an unbiased way. LCSs typically employ many scenario questions, describing hypothetical consumers and their medical situations in order to test the ability of the consumer to apply the information from the label.

Ultimately, LCSs assess comprehension, and not behavior. Therefore, LCSs are usually necessary as the foundation of successful nonprescription development programs. If a proposed label does not facilitate sufficient comprehension by consumers, it is far less likely that consumers would then be able to correctly self-select and use the product in a safe and efficacious manner. Therefore, ideally LCS provides a foundational opportunity to optimize the label before any other necessary studies are conducted.

4.2 Label Comprehension Study

FDA designed and assessed comprehension of two versions of a model naloxone DFL for use by industry to support a nonprescription drug application[17, 18]. The model naloxone DFL was validated for use in the CONFER Pivotal Label Comprehension Study.[19] The design and results of the study are summarized below. The full FDA review of the study report is also available (Cohen et al. 2020).

4.3 Design and Conduct of the Study

The study consisted of three tasks completed sequentially. In Task 1 of this study, FDA clinicians and communications experts, in consultation with outside experts in addiction treatment, developed a draft DFL. This draft DFL had simple language and adjacent pictograms. It was tested in iterative, qualitative one-on-one testing in two groups of potential consumers. One as an "all comers" group and the other was a group of those recovering from substance abuse. As a result of the findings of this phase, the DFL was revised to facilitate optimal comprehension. Task 2 of the study encompassed a pilot LCS of the model DFL to establish sample size and evaluate comprehension of the LCS questions. Task 3, the pivotal LCS, is the focus of the rest of this section.

This single-visit pivotal LCS was conducted from May to August 2018. Participants represented different geographic regions in the United States with ages spanning 15 years and above. The overall study had a total of 710 participants who completed the study interview. Specifically, 430 adults who used opioids (heroin and prescription opioids) as well as adult family members and friends of those who used opioids were recruited from community-based organizations, online advertisements, and participant referral in San Francisco; Chicago; Charleston, West Virginia; and Raleigh-Durham/Vance County, North Carolina. A total of 280 all-comer adults (ages ≥18 years) and adolescents (ages 15 to 17 years) were recruited from the general population by marketing research firms in Tampa, Dallas, Los Angeles, Raleigh, Durham, and New York City, by sites with experience recruiting limited literacy populations.

To reflect the two approved forms of naloxone available in consumer-friendly format at the time the research was designed (nasal spray and autoinjector), two model DFLs were prepared with pictograms for each dosage form. The DFL section related to the particular dosage form (Step 2 of the Directions Section) was included as a placeholder and was not tested as part of the study. The remaining content was identical for both DFL versions for naloxone. The model DFL for the nasal spray is shown in Figure 8.

In the first part of the pivotal LCS, a cognitive walkthrough method was utilized to allow the participant to talk out the sequential action steps outlined in the DFL. The cognitive walkthrough was included because of the unique labeling, which included a sequence of critical actions that needed to be undertaken immediately in an emergency situation. This is not typical of a nonprescription product. The cognitive walkthrough enabled the participants to describe the process more naturally and was intended to help the interviewer more accurately discern whether participants understood the step-wise sequence involved in the administration of naloxone. Participants were asked to imagine that they were in a situation in which they had to use the product on a friend and to state how they would do this, based on the instructions on the label. The interviewer documented the steps mentioned in the walkthrough as well as the order in which they were mentioned. This was followed by a more standard label comprehension interview that included mainly open-ended questions involving third party scenarios.

[17] https://www.fda.gov/media/119743/download
[18] https://www.fda.gov/media/119744/download
[19] https://www.fda.gov/media/119745/download

Table 6 lists the primary and secondary communication endpoints. For the primary endpoints, the a priori associated target lower bound thresholds are displayed. Secondary endpoints do not have associated thresholds.

Table 6. Primary and Secondary Endpoints

Primary Endpoint[1]	**Threshold (%)**
Step 1: Check for a suspected overdose	85
Step 2: Give the first dose of this medicine	85
Step 3: Call 911 immediately	90
Composite of Steps 1-3: Check for a suspected overdose, give the first dose of this medicine, and call 911 immediately	85
Step 4: Repeated doses every few minutes until the person is fully awake or until emergency personnel arrive	85
Step 5: Stay with the person until the emergency personnel arrive	85
Product use: Treatment of opioid overdose	80
Signs of overdose: If you think someone used an opioid and the person won't wake up or is not breathing well, these are signs of an overdose	80
Secondary Endpoints[2]	**Threshold (%)**
Note that some people may have symptoms when they wake up, such as shaking, sweating, having nausea, or feeling angry	N/A
Note that it is safe to keep giving doses	N/A
Give another dose if the person becomes very sleepy again	N/A
Make sure that the "call 911" step is completed in the appropriate order relative to the other steps	N/A
Perform steps 1-5: check for a suspected overdose, give the first dose, call 911 immediately, repeat doses every few minutes, stay with the person until the ambulance arrives	N/A

Source: FDA reviewer.
[1] The target threshold for these endpoints was set at the specified value for the lower boundary of the 95% confidence interval of the point estimate.
[2] No target thresholds were set for the secondary endpoints.
Abbreviation: N/A, not applicable

Since "Call 911" was determined by FDA to be the most important endpoint, it was assessed at a higher prespecified threshold of 90% than the others. Call 911 was recognized as most important, as in an overdose situation, the bystander's role is to get the unconscious individual into the hands of a healthcare professional as quickly as possible while delivering life-saving treatment. Naloxone alone may not be enough for a successful resuscitation.

The remaining four labeled steps, as well as the composite of steps 1 to 3 were assessed at an a priori threshold of 85%, given their slightly lower level of importance as compared to calling 911. Two other labeled statements concerning product use and overdose signs were also determined to be important enough to be primary objectives but not as important as the others; therefore, those thresholds were set at 80%.

4.4 Demographics of the Label Comprehension Population

A total of 720 participants was initially enrolled in the study and 710 completed the interview. As shown in Table 7, this included 473 normal literacy participants (66.6%) and 237 LL participants (33.4%). Of the 710 participants, there were 51% males and 49% females. The mean age of the participants was 41.6 years in the adult opioid user and associated population, 47.2 years in the all-comers population, and 16 years in the adolescent user group, with 20% of the study population younger than 18 years.

Participants were predominantly white (65%) and African American (31%); approximately 10% were Hispanic.

Table 7. Demographics of the Study Population

Variable	Overall n (%)	Normal Literacy n (%)	Limited Literacy n (%)
REALM category			
Limited literacy	237 (33.4%)	0 (0.0%)	237 (100.0%)
Normal literacy	473 (66.6%)	473 (100.0%)	0 (0.0%)
User segment			
Opioid user/associate (Groups 1, 2)	430 (60.6%)	294 (62.2%)	136 (57.4%)
Adolescent all comers (Group 3)	140 (19.7%)	88 (18.6%)	52 (21.9%)
Adult all comers (Group 4)	140 (19.7%)	91 (19.2%)	49 (20.7%)
Highest education level			
Less than high school	93 (16.3%)	42 (10.9%)	51 (27.6%)
High school graduate	227 (39.8%)	143 (37.1%)	84 (45.4%)
Some college (no degree)	140 (24.6%)	110 (28.6%)	30 (16.2%)
Postsecondary nondegree award	17 (3.0%)	15 (3.9%)	2 (1.1%)
Two-year college degree	14 (2.5%)	6 (1.6%)	8 (4.3%)
Four-year college degree	28 (4.9%)	23 (6.0%)	5 (2.7%)
Some postgraduate	34 (6.0%)	30 (7.8%)	4 (2.2%)
Postgraduate degree	17 (3.0%)	16 (4.2%)	1 (0.5%)
Hispanic or Latino			
Yes	70 (9.9%)	43 (9.1%)	27 (11.4%)
No	638 (89.9%)	428 (90.5%)	210 (88.6%)
Prefer not to answer	2 (0.3%)	2 (0.4%)	0 (0.0%)
Race (multiple responses allowed)			
White	464 (65.4%)	365 (77.2%)	99 (41.8%)
Black or African American	221 (31.1%)	89 (18.8%)	132 (55.7%)
American Indian/Alaska Native	20 (2.8%)	17 (3.6%)	3 (1.3%)
Asian	5 (0.7%)	5 (1.1%)	0 (0.0%)
Native Hawaiian/other Pacific Islander	5 (0.7%)	4 (0.8%)	1 (0.4%)
Prefer not to answer	20 (2.8%)	14 (3.0%)	6 (2.5%)
2017 Household income			
Less than $20,000	344 (60.4%)	216 (56.1%)	128 (69.2%)
$20,000-$34,999	93 (16.3%)	65 (16.9%)	28 (15.1%)
$35,000-$49,999	30 (5.3%)	24 (6.2%)	6 (3.2%)
$50,000-$74,999	31 (5.4%)	25 (6.5%)	6 (3.2%)
$75,000-$99,999	23 (4.0%)	19 (4.9%)	4 (2.2%)
$100,000-$149,999	11 (1.9%)	10 (2.6%)	1 (0.5%)
$150,000 or more	12 (2.1%)	11 (2.9%)	1 (0.5%)
Prefer not to answer	21 (3.7%)	12 (3.1%)	9 (4.9%)
Don't know	5 (0.9%)	3 (0.8%)	2 (1.1%)
Gender			
Male	359 (50.6%)	218 (46.1%)	141 (59.5%)
Female	351 (49.4%)	255 (53.9%)	96 (40.5%)
Age (years)			
Mean (SD)	37.6 (15.6)	36.6 (14.8)	39.7 (17.0)
Minimum	15.0	15.0	15.0
Median	36.5	35.4	41.8
Maximum	79.0	79.0	76.0

Variable	Overall n (%)	Normal Literacy n (%)	Limited Literacy n (%)
Age (categorical, years)			
Younger than 18	140 (19.7%)	88 (18.6%)	52 (21.9%)
18 to 24	35 (4.9%)	25 (5.3%)	10 (4.2%)
25 to 34	133 (18.7%)	103 (21.8%)	30 (12.7%)
35 to 44	150 (21.1%)	116 (24.5%)	34 (14.3%)
45 to 54	137 (19.3%)	80 (16.9%)	57 (24.1%)
55 to 64	84 (11.8%)	46 (9.7%)	38 (16.0%)
65 or older	31 (4.4%)	15 (3.2%)	16 (6.8%)
Normally wearing corrective lenses, contacts, or glasses to read	309 (43.5%)	202 (42.7%)	107 (45.1%)
Total	710	473	237

Source: FDA reviewer.
Abbreviations: n, number of subjects with a given variable; REALM, Rapid Estimate of Adult Literacy in Medicine; SD, standard deviation

4.5 Primary Endpoints: Results

As Table 8 depicts, among the eight primary endpoints, six met or exceeded the prespecified target threshold. The primary endpoint that did not meet the 90% threshold was "Call 911 immediately." Analyses of the interview transcripts revealed that most of those who answered incorrectly did refer to the "call 911" statement but did not specify that they would call immediately after the first dose. Common reasons for incorrect responses included statements that they would call 911 only if the person did not wake up; if the person did wake up; or after waiting to see if the dose worked. An additional 25 participants did not mention calling 911. Participants with lower comprehension were more likely to have limited literacy, lower educational attainment, to be black, or to be unfamiliar with naloxone.

The other primary endpoint that did not meet its threshold was the composite of the first three steps. The majority of incorrect responses were due to not calling 911 or calling 911 after waiting. Reasons unrelated to the failure to mention "call 911" include not mentioning checking on the person at all; not mentioning administering a dose; and mentioning administering a dose before checking on the person.

Table 8. Primary Endpoints: Results

Primary Endpoint	Target LB Threshold	Overall N=710 Correct Response % (LB, UB)	Normal Literacy N=473 Correct Response % (LB, UB)	Limited Literacy N=237 Correct Response % (LB, UB)
Step 1: Check for a suspected overdose	85	95.8 (94.0, 97.1)	97.9 (96.1, 99.0)	91.6 (87.3, 94.8)
Step 2: Give the first dose of this medicine	85	98.2 (96. 9, 99.0)	99.8 (98.8, 99.9)	94.9 (91.3, 97.4)
Step 3: Call 911 immediately	90	90.3 (87.9, 92.4)	94.7 (92.3, 96.6)	81.4 (75.9, 86.2)
Composite of steps 1-3	85	81.1 (78.0, 83.9)	87.9 (84.7, 90.7)	67.5 (61.2, 73.4)
Step 4: Repeated doses every few minutes until the person is fully awake or until emergency personnel arrive	85	93.8 (91.8, 95.5)	97.3 (95.4, 98.5)	86.9 (81.9, 90.9)
Step 5: Stay with the person until the emergency personnel arrive	85	91.1 (88.8, 93.1)	95.1 (92.8, 96.9)	83.1 (77.7, 87.7)
Use for treatment of opioid overdose	80	96.5 (94.9, 97.7)	98.1 (96.4, 99.1)	93.2 (89.3, 96.1)
Signs of overdose	80	94.5 (92.6, 96.1)	98.1 (96.4, 99.1)	87.3 (82.4, 91.3)

Source: FDA reviewer.
Abbreviations: LB, lower bound; N, number of subjects; UB, upper bound

4.6 Secondary Endpoints: Results

There were five secondary endpoints. As Table 9 shows, in the total analysis population (N=710), point estimates (PEs) for four of the secondary endpoints were 80% or higher. Scores for the secondary endpoints ranged from 74.6% to 95.6%, as follows:

- Safe to keep giving doses (95.6% PE)
- Give another dose if the person becomes very sleepy again (92.3% PE)
- Order of the "call 911" step (85.2% PE)
- Some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry (82.4% PE)
- Steps 1 to 5 (check, give a dose, call 911, watch and give, stay) – composite objective (74.6% PE). Common reasons for the 180 incorrect responses for the composite objective were as follows:
  - Mentioned only four of the five steps – 53.9%; 97 of 180
  - Mentioned only three steps – 25.0%; 45 of 180

The results indicated that these messages were adequately understood by the participants with point estimates exceeding 80% for all secondary endpoints with the exception of the composite score for getting all five steps correct (74.6% PE). More than half of the incorrect participants stated four of the five steps correctly (53.9%), and more than three quarters of the incorrect participants stated at least three of the five steps (78.9%). Importantly, of the participants who mentioned at least three steps,

nearly all of them (84.5%) mentioned the two important interventions of checking the victim for an overdose and giving a first dose.

Table 9. Secondary Endpoint Result

Secondary Endpoint	Point Estimate
It is safe to keep giving doses	95.6%
Give another dose if the person becomes very sleepy again	92.3%
Order of the "call 911" step	85.2%
Some may experience symptoms when they wake up, such as shaking, sweating, nausea or feeling angry	82.4%
Steps 1-5 (check, give a dose, call 911, watch and give, stay) composite objective	74.6%

Source: FDA reviewer.

4.7 Qualitative Endpoints: Results

Two qualitative endpoints were also explored to assess whether participants reported the specific time required to wait before redosing, as well as how well the term "opioid" was understood.

- Wait 2 to 3 minutes between doses: nearly all (95.1%) participants provided at least one response in the cognitive walkthrough or one of the predetermined comprehension questions that specified waiting 2 to 3 minutes between giving doses; 3.2% did not mention a time, and 1.3% referenced 1.5 to 4 minutes or a few/couple minutes.
- What is an opioid: Participants provided varying responses when asked for the definition, but the majority did correctly understand the drug categories for which naloxone is effective. The most common responses were: heroin; pain medicine; type of drug (nonspecific); prescription pain medication; drug with opiates.

5 Study to Support the Indication - Human Factors Validation Study

5.1 Human Factors Overview

When a nonprescription drug product is proposed for use with a device, HF studies (FDA 2016) may be conducted to ensure the user interface[20] is optimized to maximize the likelihood the product will be used safely and effectively by the intended users, for the intended users, and for the intended use environments. Prior to designing and conducting a human factors study, Applicants should conduct a comprehensive use-related risk analysis. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using the product (e.g., based on a task analysis), the errors that users might commit, or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. The use-related risk analysis should also discuss risk-mitigation strategies employed to reduce risks identified and the methods intended to validate the risk-mitigation strategies. The use-related risk analysis is then used to inform the design of an HFVS protocol.

HFVSs are studies conducted under simulated use conditions with representative users performing necessary tasks to assess the adequacy of the product user interface design. The results of these studies should be analyzed qualitatively to determine if the design of the user interface needs to be modified to

[20] The term *user interface* refers to all components of the product with which the user interacts, including the device constituent part(s) of the product and any associated controls and displays, as well as product labels, labeling, and packaging.

reduce the use-related risks to acceptable levels. Ideally, the final intend-to-market user interface is tested under simulated methods (e.g., placebo-filled device administered to a manikin in a setting that mimics real world use conditions) to demonstrate that intended users are able to perform the steps necessary for safe and effective use of the product. The conditions of the HFVS should be sufficiently realistic so that the results can be extrapolated to actual use of the product once introduced into the market. Tasks to be performed in the HF simulated-use validation study should include those critical tasks identified in a use-related risk analysis.

Much like the LCS, HF studies are part of an iterative design process that should start with preliminary analyses, including formative studies, of a combination product prototype to identify potential use errors and inform the need for user interface changes. The objective of a validation study is to demonstrate that the final finished combination product user interface supports safe and effective use of the product by intended users, for intended uses, and under the expected conditions.

If use errors or problems (e.g., failures, "close calls," use difficulties) are identified in an HFVS, each should be evaluated to (1) identify the root cause(s), (2) determine the potential for harm (including the clinical significance of such errors or problems and the potential for compromised medical treatment), and (3) determine whether additional measures to eliminate or mitigate risks are necessary. When reviewing study results it is important to note that human factors validation testing is primarily a qualitative rather than a quantitative exercise. The goal is to evaluate users' interactions with a device user interface by observing their performance and simultaneously collecting subjective user assessments of their experience using the device to assess the adequacy of the user interface design. Use errors are recorded but the purpose is not to quantify the frequency of any particular use error or establish acceptability with respect to numerical acceptance criteria. Instead, the purpose is to identify the part of the user interface involved in a use error or problem and investigate the causes of the use error or problem so that the design of the user interface can be optimized for safe and effective use. The root causes of all use errors and problems should be considered in relation to the associated risks to ascertain the potential for resulting harm and determine the priority for implementing additional risk management measures. As a general practice, design modifications made in response to human factors validation testing results to eliminate or reduce unacceptable use-related risks should be evaluated in a subsequent test to determine whether the design modifications were effective and whether they have introduced unacceptable new risks that need to be eliminated or reduced.

5.2 HVFS

The Applicant included a HFVS in the submission to support the proposed nonprescription switch. The study was conducted without seeking review and guidance from FDA on the study protocol or methodology. The HFVS is intended to provide data to support safe and effective use of the nonprescription product by adolescents and adult lay people (friends, family, bystanders, caregivers) without medical training who may encounter someone experiencing an opioid overdose and acquire or purchase the proposed product without the supervision of a licensed healthcare provider. The dosing of the nonprescription product are the same as for the prescription product—one spray intranasally into one nostril, administering additional doses using a new nasal spray every 2 to 3 minutes until the person wakes up. Although the drug product and delivery device are identical to the prescription NNS, a HFVS is necessary because the Applicant developed new packaging and labeling for the nonprescription NNS to address the different conditions of use in the nonprescription setting compared to prescription community use, representing a new user interface that has never been tested for performance by the intended users.

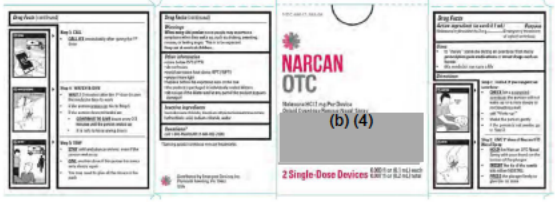
In the HFVS, the Applicant evaluated a mock carton to represent the nonprescription NNS user interface, which was designed to include the FDA model nasal spray DFL embedded with the nonprescription NNS product-specific instructions.

It is important to note that the **mock** carton tested in the HFVS differs from the Applicant's proposed **intend-to-market** carton. Thus, care is taken throughout this section to refer to the HFVS tested carton as the mock carton and the carton proposed for marketing as the intend-to-market carton.

Relevant aspects of the mock carton tested include:

- The mock carton's DFL Directions section is divided across two carton panels that are viewable only after rotating the carton box (i.e., the back panel of the mock carton depicts Steps 3, 4, and 5, whereas the side panel depicts Steps 1 and 2). This is in contrast to the approved prescription NNS carton, which has a flap that opens up to instructions on the same viewable surface. See Figure 5 for associated images.
- The figures and text for steps 1, 3, 4, and 5 of the proposed NNS DFL Directions Section are identical to the FDA model DFL Directions previously assessed in FDA's CONFER study.
- Step 2 of the proposed NNS DFL Directions replaces the FDA model DFL "placeholder" Step 2 Directions with product-specific instructions on how to give the first dose.
- The prescription NNS blister packaging includes a QSG whereas the QSG has been removed from the nonprescription NNS blister packaging. See Figure 5 for associated images.

Figure 5. Comparison of User Interface Between the Mock NNS Carton and Prescription NNS

Nonprescription Mock Narcan Carton	Prescription Narcan Carton
DFL Directions divided across 2 panels - need to rotate carton to view Steps on another panel 	Flap on the front of the carton that opens up to display all Steps instructions on the same viewable surface 
Blister Packaging does not contain a QSG 	Blister Packaging contains a QSG 

Source: Current Applicant supplementary submission (DailyMed).
Abbreviations: DFL, Drug Facts Leaflet; NNS, Narcan Nasal Spray; QSG, Quick Start Guide

5.3 Study Methods

The study evaluated 71 untrained participants representing four user groups.

- Adult general population ("all comers", age 18 years and older).
- Adolescents (age 15 to 17 years).
- Adult opioid users (age 18 years and older).
- Adult opioid user associates (age 18 years and older).

Participants were provided with a "mock" nonprescription NNS carton that displayed the proposed DFL. Inside the carton were two blister-packaged units each containing one NNS (placebo-filled). Participants were told to review and familiarize themselves with the product labeling and then demonstrate or verbally describe how they would administer the medicine to treat a family member, represented by a manikin, who had overdosed with pain medication. Participants were allowed as much time as needed to review the "mock" carton and DFL (i.e., participants were given a familiarization period). Then, participants were asked to demonstrate administration of the product in a simulated overdose situation in the presence of an observer (i.e., study moderator). The study moderator also informed participants: "if you'd like to you can also verbally tell me what you are doing or would do as you complete the demonstration" (i.e., encouraged to use a "think aloud" method). During and following the simulation, the study moderator asked the participants questions about any steps or actions that they failed to perform correctly. Interviews were recorded and the study moderator scored each performance in real

time as correct, acceptable, incorrect, or could not be observed. For selected steps, if participants failed to perform the step but clearly articulated the procedure, they were scored as acceptable. After completion of the interviews, all recordings were transcribed and coded verbatim responses were used for analysis of study endpoints.

The Applicant reported study results as correct, acceptable, or incorrect using **quantitative** thresholds for success (e.g., percentage acceptable). However, generally HFVS are not intended to provide quantitative information on primary, secondary, or composite outcomes.[21] The results of these studies should be analyzed **qualitatively**, using information gathered from every occurrence of use error (UE)[22], use difficulty (UD)[23], and close call (CC).[24] The direct observations of participant performance and interaction with the product, subjective user feedback, and root cause analysis from the study provide valuable qualitative data that can identify vulnerabilities with the design of the user interface, and inform appropriate mitigations for the interface design. With this submission, the HFVS report did not include the complete qualitative data sets, such as the root cause analysis and participants' subjective feedback for all use errors. Additionally, data on UD and CC were not submitted.

Thus, in the initial phase of review, FDA issued information requests to obtain the complete qualitative data sets. The results from the qualitative data sets were provided by the Applicant and form the basis for the results and analysis included in this document. Additional details pertaining to the HFVS methodology are contained in Table 10.

Table 10. Study Methodology for HFVS

Study Design Elements	Details from the Applicant's HFVS Results Report
Participant	71 participants in the following user groups:[25] • Adult general population (all comers), age 18 years or older (n=18) — 22.2% LL • Adolescent, ages 15-17 years (n=19) — 36.8% LL • Adult opioid users, age 18 years or older (n=16) — 31.3% LL • Adult opioid user associates, age 18 years or older (n=18) — 27.8% LL

[21] Human factors validation testing is primarily a qualitative rather than a quantitative exercise. The goal is to evaluate users' interactions with a device user interface by observing their performance and simultaneously collecting subjective user assessments of their experience using the device to assess the adequacy of the user interface design. FDA 2016, Guidance for Industry and FDA Staff; Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-factors-studies-and-related-clinical-study-considerations-combination-product-design-and

[22] Use error is defined as user action or lack of action that was different from that expected by the manufacturer and caused a result that (1) was different from the result expected by the user and (2) was not caused solely by device failure and (3) did or could result in harm.

[23] A use difficulty is defined as a difficulty, or struggle, encountered during use, which is typically momentary and overcome by the user.

[24] Close call is defined as instances in which a user has difficulty or makes a use error that could result in harm, but the user takes an action to recover and prevents the harm from occurring.

[25] Based on the Applicant's information request response dated December 9, 2022, three participants (# (b) (6) - (b) (6)) verbally described tasks instead of performing tasks. Therefore, the HFVS includes simulated use performance data for 68 participants.

Study Design Elements	Details from the Applicant's HFVS Results Report
Training	Participants were untrained, but given an unlimited familiarization time period (see the *Sequence of Study* row below)
Test environment	In order to help simulate the stress and distractions found in a real-world environment, a television in the interview room was playing a movie in the background.
Test materials	All participants were provided with a mock nonprescription product in carton with a DFL. Inside the carton were two blister-packaged units each containing one NNS, which contained water or saline solution only. The nasal spray device was identical to the NNS device that is currently manufactured and distributed.
Sequence of study	• Pre-interview activities — Consumers who met initial eligibility criteria scheduled an appointment to complete a brief literacy assessment remotely via audio/video interface with a trained interviewer prior to scheduling an interview at the site • Rapid Estimate of Adult Literacy in Medicine (REALM)/REALM-Teen Test administered via audio/video interface to characterize participants' health literacy • Rescreening to verify eligibility • Informed consent • Recording initiated • The participant was told that their task was to review the product labeling and to then use the provided medicine and product directions to treat a family member, represented by a manikin, who had overdosed with pain medication. • Participants were allowed as much time as needed to review the mock nonprescription product and its DFL, and then were asked by a trained interviewer to demonstrate administration of the product in a simulated overdose situation. — Moderator script includes the following: "If you'd like to you can also verbally tell me what you are doing or would do as you complete the demonstration." • Questions were asked to assess comprehension of any directions for use that the participant failed to perform correctly (or in the case of prespecified tasks, to clearly articulate the procedure verbally) in the demonstration portion of the interview. Per the Applicant, this explanation by participants enabled the assessment of whether the participant comprehended the instruction, and only failed to demonstrate the task correctly during the demonstration portion due to limitations of the simulation process. • Debriefing questions: — The interviewer next asked debriefing questions about any steps/actions that were performed incorrectly or not comprehended

Study Design Elements	Details from the Applicant's HFVS Results Report
Data collection and analysis	• Interviews were recorded • The interviewer scored each performance in real time as it was demonstrated as correct, acceptable, incorrect, or could not be observed • For selected steps, if participants did not perform the step or performed it incompletely, but clearly articulated the procedure they would intend to follow, their performance may have been scored as acceptable. • Responses to debriefing questions were also collected • After completion of interviews, all recordings were transcribed, and coded verbatim responses were used for analysis of study endpoints

Source: FDA review and summary.
Abbreviations: DFL, Drug Facts Leaflet; HFVS, human factors validation study; LL, limited literacy; N, number of subjects; NNS, Narcan Nasal Spray;

5.4 Study Limitations

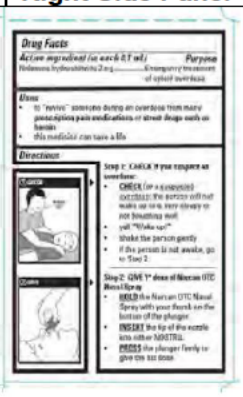
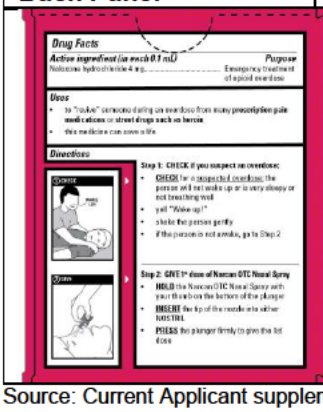
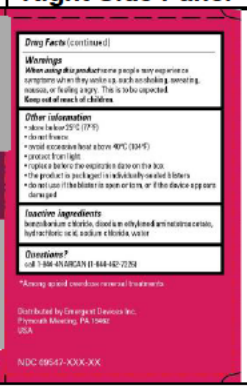
The Applicant did not submit the HFVS protocol for review and guidance prior to conducting the HFVS. Based on the design and methodology of the HF study, several study limitations must be taken into consideration when interpreting the study results.

- Pediatric users 10 to 14 years old who may administer the proposed product to revive someone during an overdose were not tested; therefore, the data collected may not be generalized to this untested age range of the adolescent user group.
  - The Applicant states that the intended users of the product include adolescents and adults. The HFVS included pediatric participants 15 to 17 years old; however, FDA has identified cognitive and moral development in children as young as 10 years of age that can perform mental operations and thoughts using formal concrete concepts (Hollan-Hall and Burstein 2016). Thus, we generally recommend the HFVS include pediatric participants 10 to 17 years old. Because pediatric users between 10 to 14 years old were not tested, the data collected may not be generalized to the untested age range of the adolescent user group.
- Two user groups did not include at least 30% LL participants which may have introduced bias with tendency towards positive performance in the affected user groups.
  - The HFVS did not include at least 30% LL participants in two of the four user groups (the Adult General Population (22.2% LL participants) and Adult Opioid User Associates (27.8%) user groups); however, 30% of the total combined participants were LL participants. For HF testing in nonprescription products, we generally recommend that each distinct user group include 30% LL participants to ensure adequate representation of the intended users in the study. The distribution of LL participants may have introduced bias with tendency towards positive performance in the affected user groups (i.e., Adult General Population and Adult Opioid User Associates), which should be taken into consideration when interpreting the study results.
- Participants were allowed an unlimited familiarization period, which is not representative of the high risk scenario where users may have limited time to interact with product labeling and act quickly during an overdose event.
  - All participants in the HFVS were allowed as much time as needed to review the product labeling before demonstrating use of the product in a simulated overdose situation (i.e., "familiarization

period"). While we acknowledge that some users may have the opportunity to familiarize themselves with the product labeling before administration of the product, some users may have limited time to interact with the product labeling when encountering an opioid overdose emergency situation during actual use. Thus, we generally recommend that, at a minimum, some user groups in the HFVS simulate a scenario that is representative of a high-risk actual use event (e.g., no familiarization prior to encountering overdose emergency). In light of the familiarization period used in the study, the data collected does not capture the highest risk use scenario.

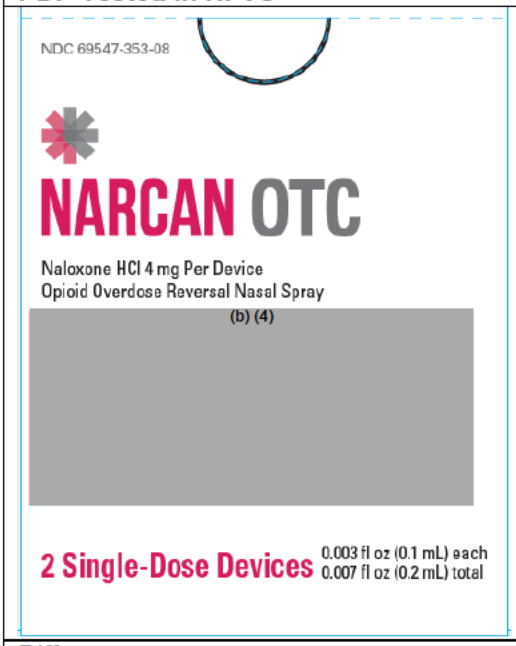
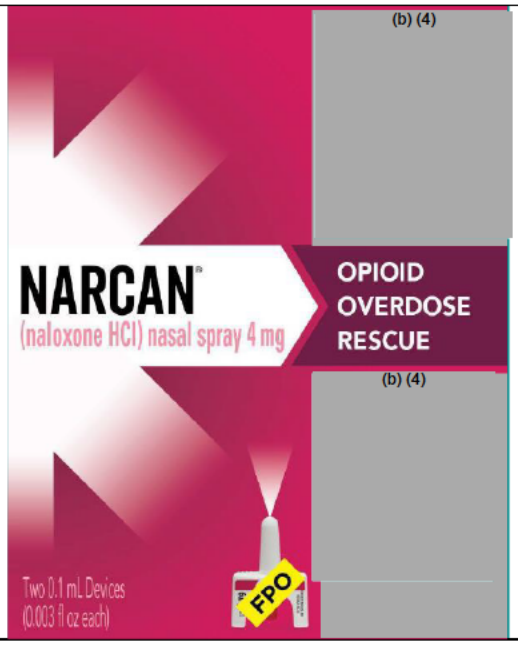
- Moderators employed use of leading language and the "think aloud" method, which is not reflective of a real life scenario and may have influenced participant behavior/performance.
  - Participants in the HFVS were instructed by the study moderator to, "Please use the package directions" prior to demonstrating use of the product in a simulated overdose scenario. Use of leading language might impact study participant performance and is not representative of actual use (i.e., it's unlikely someone will instruct or remind a user to use the packaging directions during actual use).
  - The moderator script included language for participants to verbally state what they are doing or what they would do as they complete the simulated use scenario. Instructing participants to think aloud is not representative of actual use, and it interrupts the natural sequence and flow of events. Additionally, it may confound the results by affecting how the participant completes the task.
  - We generally recommend that the moderator refrain from using leading language and avoid encouragement of a think aloud method as such methods may have introduced a bias towards positive performance, which should be taken into consideration when interpreting the HFVS results.
- The mock carton labeling tested in the HFVS differs from the intend-to-market carton labeling, which raises questions as to whether the study results can be used to support the intend-to-market labeling (see Table 11 and Table 12).
  - The mock carton labeling evaluated in the HFVS is different from the intend-to-market carton labeling submitted. Most notably, the mock carton labeling tested in the HFVS displays Steps 3, 4, and 5 of the DFL Directions on the back panel; whereas the intend-to-market carton labeling has been modified post-HF validation in response to the HFVS results, such that Steps 1 and 2 of the DFL Directions are on the back panel. Some changes appear to be cosmetic in nature and not specifically intended for risk mitigation (e.g., colors, branding, etc.); while other changes to the PDP include different statements, relocation of important statements, and/or changes to font size of important statements. We generally expect the HFVS evaluate the intend-to-market user interface, including labels and labeling. Changes to formatting, layout, text size, color, etc. may impact users' performance of critical tasks.

Table 11. Mock Carton Tested in the HFVS Versus Intend-to-Market Carton Submitted

Mock Carton Tested in HFVS			
Back Panel	**Left Side Panel**	**PDP**	**Right Side Panel**
			
Intend-to-Market Carton Submitted September 29, 2022			
Back Panel	**Left Side Panel**	**PDP**	**Right Side Panel**
			

Source: Current Applicant supplementary submission.
Abbreviations: HFVS, human factors validation study; OTC, over-the-counter; PDP, principal display panel

Table 12. Mock Carton PDP Tested in HFVS Versus Intend-to-Market Carton PDP

PDP Tested in HFVS	Intend-to-Market PDP
	

Differences:

- Updated the PDP to a more consumer friendly packaging feel, including the following:
  - Updated primary color from white to pink.
  - Added a graphic of the nasal sprayer.
  - Updated the indication statement and product claims based on language widely understood by consumers (i.e., based on results from market research).
- Updated the statement of identity to comply with 21 CFR 201.61(b) and the Draft FDA Guidance for Industry[1].
- Updated the net contents statement to comply with 21 CFR 201.62(a), (c), and (d)
- Moved the National Drug Code from the PDP to the side panel.
- Change in font color from pink to white.
- Relocation and decreased font size of the statement, "2 Single-Dose Devices."

Source: Source: FDA review and summary.
[1] FDA (2022b)
Abbreviations: CFR, Code of Federal Regulations; HCl, hydrogen chloride; HFVS, human factors validation study; OTC, over-the-counter; PDP, principal display panel

5.5 Summary of Qualitative Results

FDA reviewed the qualitative data set provided by the Applicant (not originally included with the submission) including all UEs, CCs, and UDs. We also reviewed all subjective feedback from participants collected by the Applicant (if available), the Applicant's root cause analysis for each error (when provided), and the Applicant's proposed mitigations. The full qualitative data set provided by the Applicant is shown in Table 14. A high-level summary of the results is provided in Table 13.

Table 13. High-Level Summary of HFVS Results for Steps 2, 3, and 4

Seventy-one participants[1] in the following user groups: **General population:** Adult general population (all comers), age 18 years or older (n=18) **Adolescent:** Adolescent, ages 15-17 years (n=19) **Opioid user:** Adult opioid users, age 18 years or older (n=16) **Opioid user associates:** Adult opioid user associates, age 18 years or older (n=18)			
Step	**Number of Use Errors (UE)**	**Number of Close Calls (CC)**	**Number of Use Difficulties (UD)**
Step 2: GIVE 1st dose of Narcan OTC Nasal Spray	5 UE: • Adolescent (n=3) • Opioid user (n=1) • Opioid user associate (n=1)	2 CC: • Adolescent (n=1) • Opioid user associate (n=1)	9 UD: • General population (n=2) • Adolescent (n=2) • Opioid user (n=3) • Opioid user associate (n=2)
Step 3: Call 911	10 UE: • General population (n=2) • Adolescent (n=1) • Opioid user (n=3) • Opioid user associate (n=4)	5 CC: • General population (n=4) • Opioid user (n=1)	0 UD
Step 4: Watch & Give	12 UE: • General population (n=1) • Adolescent (n=5) • Opioid user (n=2) • Opioid user associate (n=4)	0 CC	0 UD

Source: FDA review and analysis.
[1] Three participants verbally descr bed tasks instead of performing tasks. Therefore, the HFVS includes simulated use performance data for 68 participants.
Abbreviations: HFVS, human factors validation study; n, number of subjects; OTC, over-the-counter

Numerous use errors occurred in the study that can be directly attributed to the user interface (labeling and packaging design) of the "mock" carton tested in the study. Relevant findings and our recommendations for consideration by the AC panel include:

5.5.1 Relevant Finding #1

Numerous participants experienced a UE, CC, or UD in giving the first dose because these participants turned to the back panel of the carton and initiated their simulation using **Step 3** (Call 911) of the DFL "Directions", bypassing **Step 1** (Check) and **Step 2** (Give 1st Dose) which appear on the side panel of the carton. These errors indicate that the placement of the DFL directions on the "mock" carton, with Steps 1 and 2 on the side panel and Steps 3, 4, and 5 on the back panel contributed to the use errors. Use errors of this nature are likely to result in delayed administration of naloxone if users have difficulty locating where to start on the DFL Directions or understanding the sequence of the steps to give the first dose of naloxone, which may result in negative outcomes.

In response to these errors, the Applicant proposes to implement a post-HFVS revision to the intend-to-market carton by presenting **Step 1** (Check) and **Step 2** (Give 1st Dose) on the back panel; and **Step 3** (Call 911), **Step 4** (Watch & Give), and **Step 5** (Stay) on the side panel. However, it is unclear if this

mitigation will effectively address the UEs observed without introducing new risks for error. For example, we are concerned that some users may overlook Steps 3, 4, and 5 on the side panel if they remain divided from Steps 1 and 2 on the back panel. In fact, one participant, who correctly started with Step 1 and gave the first dose successfully spent 50 seconds reading the wrong face of the DFL before proceeding to Step 3 on the next panel. This UE would result in delayed arrival of emergency response healthcare personnel and/or delaying or not giving a second dose that may be needed. Furthermore, the Applicant did not propose to validate this proposed mitigation strategy; thus, there are no supporting HF data to demonstrate the proposed mitigation will address the UEs.

Proposal for AC Panel Consideration for Finding #1

The Applicant's carton design may negatively impact the safe and effective use of the product. We request that the AC consider whether redesign of the carton such that the back panel includes all five steps (Steps 1 to 5) of the DFL "Directions" uninterrupted and in the appropriate sequence may mitigate the observed use errors. Additionally, we request that the AC consider whether inclusion of a QSG within each blister package that displays Steps 1 through 5 of the DFL using text and figures consistent with the DFL Directions on a single-sided page may minimize the risk of users missing steps.

5.5.2 Relevant Finding #2

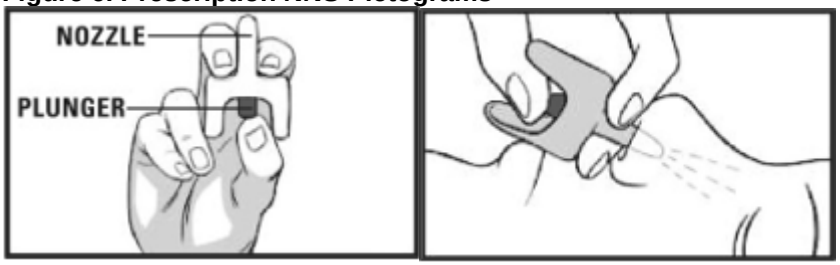
One participant experienced a UE where s/he squeezed the device without pushing the plunger and failed to administer a dose, but the root cause is unclear based on the HFVS results report because the study moderator did not probe further to understand the participant's confusion. One participant held the device inverted, with the bottom of the plunger pointing up. The participant's subjective feedback indicates that the user interface may have contributed to the use error. Specifically, the participant stated, "It just didn't say what direction to put it in." Use errors of this nature are likely to result in delayed dose or no dose of naloxone if users have difficulty activating the device, which may result in negative outcomes.

Proposal for AC Panel Consideration for Finding #2

There are two pictograms in the prescription Narcan instructions that show how to position the hand and fingers around the nasal spray (see Figure 6), whereas the hand position is shown at a different angle on the nonprescription DFL Step 2 Pictogram (see Figure 7), and may be less clear to the user.

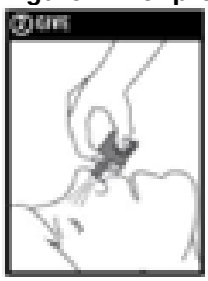
We request that the AC panel consider if the Step 2 pictogram may be further improved to optimize the nonprescription Narcan carton labeling, for example, by incorporating elements of the prescription Narcan pictogram or, alternatively, by adding a pictogram depicting the proper hand position on the carton PDP.

Figure 6. Prescription NNS Pictograms



Source: Original Applicant submission for prescription product
Abbreviation: NNS, Narcan Nasal Spray

Figure 7. Nonprescription NNS DFL Step 2 Pictogram



Source: Current Applicant supplementary submission.
Abbreviations: DFL, Drug Facts Leaflet; NNS, Narcan Nasal Spray

5.5.3 Relevant Finding #3

One participant did not keep the nozzle fully in the nostril while administering a dose, which resulted in a partial dose administration. Although the participant's subjective feedback and root cause analysis did not cite wording in the DFL as a contributing factor to the use error, the second bullet of the step states, "INSERT the tip of the nozzle into either NOSTRIL." The word *tip* may result in users not fully inserting the nozzle into the nostril, which may result in partial dose administration.

Proposal for AC Panel Consideration for Finding #3

We request the AC consider whether revision of the bullet to state, "INSERT the nozzle into either NOSTRIL" rather than "INSERT the tip into either NOSTRIL" may mitigate use error.

5.5.4 Relevant Finding #4

Several participants experienced a UE or CC because they were confused about whether each nasal spray device contained a single dose or multiple doses. For example, one participant provided the following subjective feedback, "I spent 30 seconds trying to figure out if each one of these was one dose or multiple doses. And it never said." The user interface can be improved to further minimize the risk of this use error.

Proposal for AC Panel Consideration for Finding #4

We request that the AC consider potential benefits of adding a statement that each nasal spray device contains one dose of naloxone to the container label, PDP, and Step 2 of the DFL. In addition, we request that the AC consider potential benefits of revising the carton labeling to display an image depicting two nasal spray devices to minimize confusion on the number of nasal spray devices in each carton.

6 Summary of Switch Considerations

The purpose of the Joint Nonprescription Drugs Advisory Committee/Anesthetic and Analgesic Drug Products Advisory Committee meeting is to discuss the adequacy of the data submitted by the Applicant to support the approval of NNS as a nonprescription drug product. Key data to consider include the safety data from prescription marketing and the HFVS. We look forward to input from the advisory committee on whether the data support this novel first-in-class switch, and in particular advice from the committee on further considerations to improve product labeling to ensure safe and effective use by the untrained consumer in an emergency situation.

7 References

Literature

Abdelal, R, A Raja Banerjee, S Carlberg-Racich, N Darwaza, D Ito, J Shoaff, and J Epstein, 2022, Real-world study of multiple naloxone administration for opioid overdose reversal among bystanders, Harm Reduct J, 19(1):49.

Avetian, GK, P Fiuty, S Mazzella, D Koppa, V Heye, and P Hebbar, 2018, Use of naloxone nasal spray 4 mg in the community setting: a survey of use by community organizations, Curr Med Res Opin, 34(4):573-576.

Bardsley, R, 2019, Higher naloxone dosing may be required for opioid overdose, Am J Health Syst Pharm, 76(22):1835-1837.

Brenner, DS, AI Stolbach, J Zschoche, and L Bright, 2021, Severe prolonged agitation due to intranasal naloxone overexposure, Am J Emerg Med, 42:261 e261-261 e262.

Carroll, GG, DD Wasserman, AA Shah, MS Salzman, KE Baston, RA Rohrbach, IL Jones, and R Haroz, 2021, Buprenorphine Field Initiation of ReScue Treatment by Emergency Medical Services (Bupe FIRST EMS): A Case Series, Prehosp Emerg Care, 25(2):289-293.

CDC, 2022, Provisional Drug Overdose Death Counts, accessed, https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

Cohen, BR, KM Mahoney, E Baro, C Squire, M Beck, S Travis, A Pike-McCrudden, R Izem, and J Woodcock, 2020, FDA Initiative for Drug Facts Label for Over-the-Counter Naloxone, N Engl J Med, 382(22):2129-2136.

Connors, NJ and RJ Hamilton, 2019, Withdrawal Principles, Goldfrank's Toxicologic Emergencies, Nelson, L. S., M. A. Howland, N. A. Lewin et al.: McGraw Hill.

Dezfulian, C, AM Orkin, BA Maron, J Elmer, S Girotra, MT Gladwin, RM Merchant, AR Panchal, SM Perman, MA Starks, S van Diepen, EJ Lavonas, CCP American Heart Association Council on Cardiopulmonary, Resuscitation, T Council on Arteriosclerosis, B Vascular, C Council on, N Stroke, C Council on Quality of, R Outcomes, and C Council on Clinical, 2021, Opioid-Associated Out-of-Hospital Cardiac Arrest: Distinctive Clinical Features and Implications for Health Care and Public Responses: A Scientific Statement From the American Heart Association, Circulation, 143(16):e836-e870.

Direct_Relief, 2021, Pfizer to Donate 1 Million Naloxone Doses to Direct Relief for Life-Saving Opioid Overdose Reversal, accessed January 6, 2023, https://www.directrelief.org/2021/04/pfizer-to-donate-1-million-naloxone-doses-to-direct-relief-for-life-saving-opioid-overdose-reversal/.

FDA, 2022a, FDA's Overdose Prevention Framework Aims to Prevent Drug Overdoses and Reduce Death, accessed January 9, 2023, https://www.fda.gov/news-events/fda-voices/fdas-overdose-prevention-framework-aims-prevent-drug-overdoses-and-reduce-death.

Gaither, JR, V Shabanova, and JM Leventhal, 2018, US National Trends in Pediatric Deaths From Prescription and Illicit Opioids, 1999-2016, JAMA Network Open, 1(8):e186558-e186558.

Hollan-Hall, C and G Burstein, 2016, Adolescent Development, Nelson Textbook of Pediatrics, Kliegman, R., B. Stanton, J. Geme and N. Schor, 20 edition: Elsevier, 926-936.

Kummer, RL, RR Kempainen, TD Olives, JW Leatherman, and ME Prekker, 2022, Naloxone-associated pulmonary edema following recreational opioid overdose, Am J Emerg Med, 53:41-43.

Miller, S, 2018, Narcan emergency overdose treatment added to University's AED cabinets, University of Rochester, accessed January 17th, 2023, https://www.rochester.edu/newscenter/narcan-added-to-universitys-aed-cabinets-329492/.

Nabarun, D, MD Simkins, and E Wheeler, 2021, A Thousand Ways to Say "no" to Naloxone, DOI: https://doi.org/10.17615/1vqa-gt51.

Veet, CA, N Vu, and A Kohli, 2017, Reversing Opiates in a Flash: Intranasal Naloxone-Induced Pulmonary Edema, J Gen Intern Med, 32.

Wesson, DR and W Ling, 2003, The Clinical Opiate Withdrawal Scale (COWS), J Psychoactive Drugs, 35(2):253-259.

Wheeler, E and M Doe-Simkins, 2020, Harm reduction programs distribute one million doses of naloxone in 2019, accessed, https://medium.com/@ejwharmreduction/harm-reduction-programs-distribute-one-million-doses-of-naloxone-in-2019-4884d3535256.

Yarlagadda, K, J Kim, T Kanderi, S Sendil, and VK Nookala, 2020, Opioid antidote induced pulmonary edema and lung injury, Respir Med Case Rep, 30:101107.

Guidances for Industry

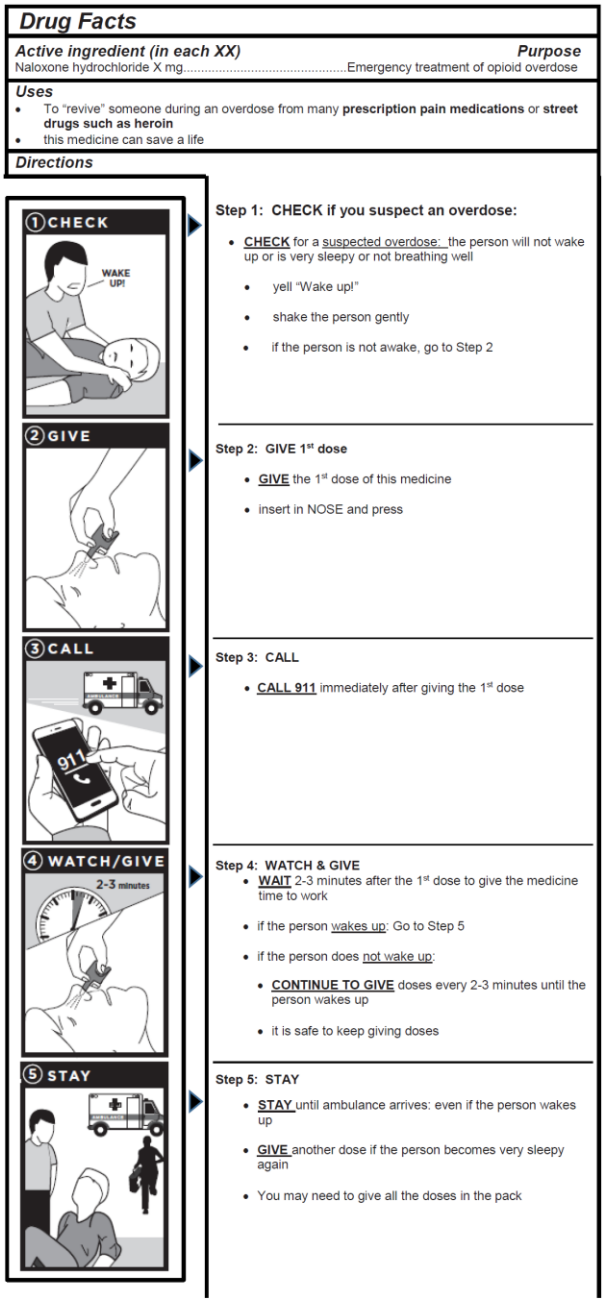
FDA, 2016, Guidance for Industry and FDA Staff; Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-factors-studies-and-related-clinical-study-considerations-combination-product-design-and.

FDA, 2022b, Guidance for Industry; Statement of Identity and Strength — Content and Format of Labeling for Human Nonprescription Drug Products, accessed December 8, 2020, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statement-identity-and-strength-content-and-format-labeling-human-nonprescription-drug-products.

8 Appendices

8.1 Model Drug Facts Label and Pictogram Assessed in the FDA CONFER Study

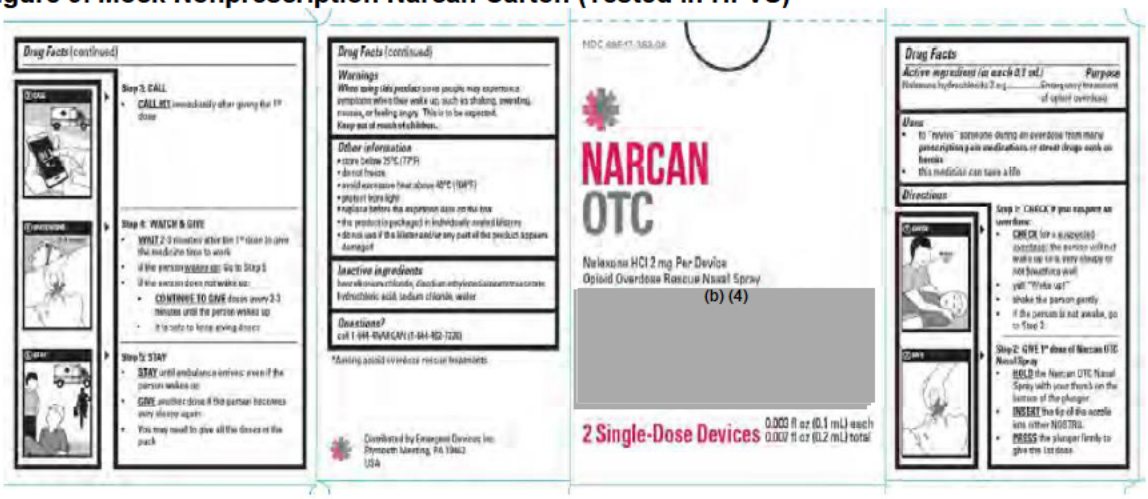
Figure 8. FDA Model Naloxone Nasal Spray Drug Facts Label and Pictogram



Source: 84 FR 8728 (March 11, 2019).

8.2 "Mock" Nonprescription Narcan Carton Tested in HFVS

Figure 9. Mock Nonprescription Narcan Carton (Tested in HFVS)



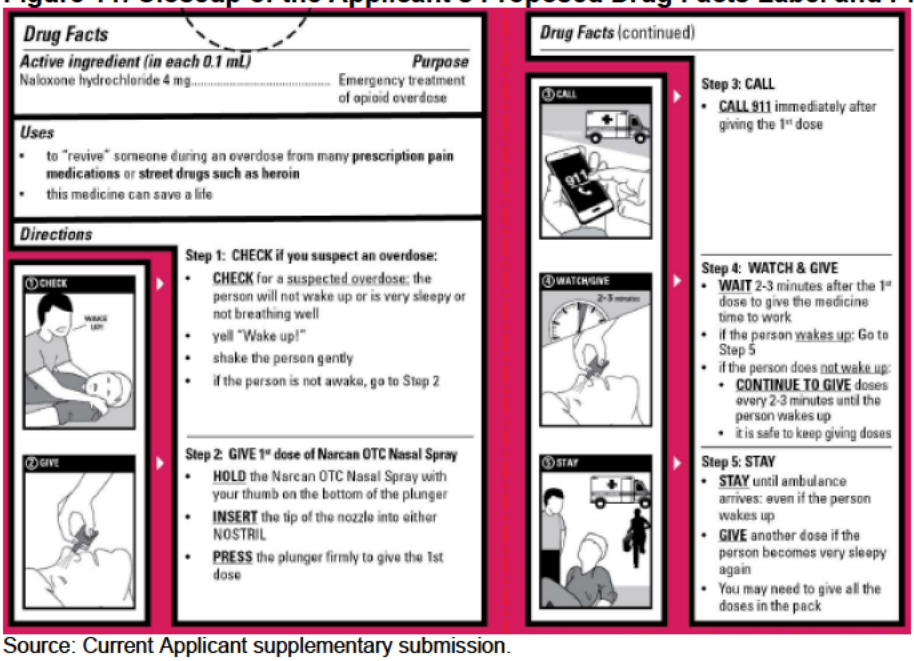
Source: Current Applicant supplementary submission.
Abbreviations: HCl, hydrogen chloride; HFVS, human factors validation study; OTC, over-the-counter

8.3 Intend-to-Market Nonprescription Narcan Carton

Figure 10. Intend-to-Market Nonprescription Narcan Carton

Source: Current Applicant supplementary submission.
Abbreviation: HCl, hydrogen chloride; OTC, over-the-counter

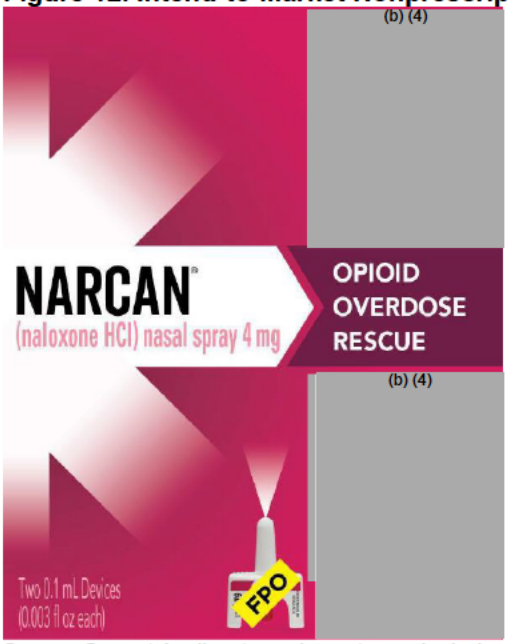
Figure 11. Closeup of the Applicant's Proposed Drug Facts Label and Pictograms



Source: Current Applicant supplementary submission.

8.4 Intend-to-Market Nonprescription Narcan Principal Display Panel (or Front of Panel for the Proposed Carton)

Figure 12. Intend-to-Market Nonprescription Narcan Principal Display Panel



Source: Current Applicant supplementary submission.
Abbreviation: HCl, hydrogen chloride

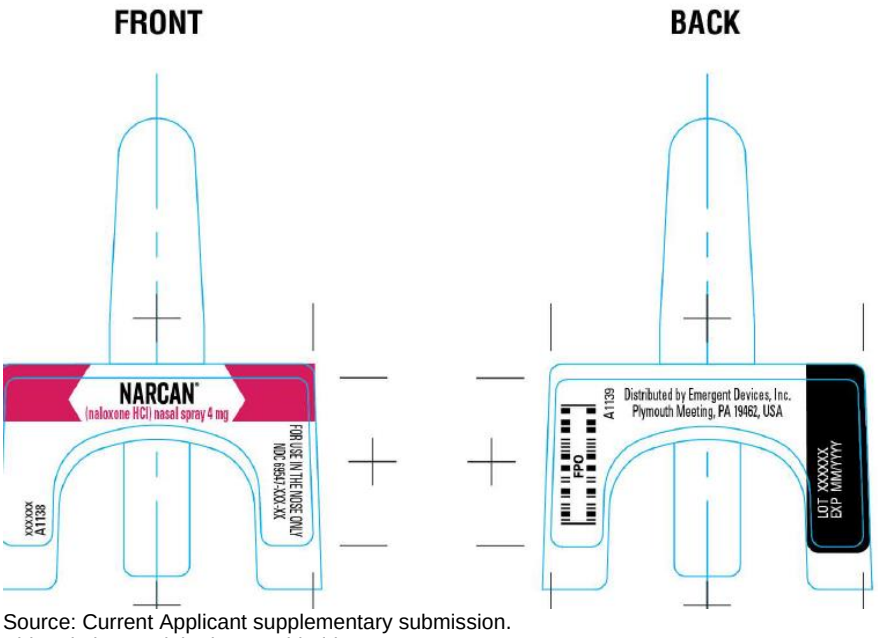
8.5 Proposed Nonprescription Narcan Blister Labeling

Figure 13. Nonprescription Narcan Blister Labeling

Source: Current Applicant supplementary submission.
Abbreviations: HCl, hydrogen chloride

8.6 Proposed Nonprescription Drug Delivery Device and Label

Figure 14. Proposed Nonprescription Drug Delivery Device and Label



Source: Current Applicant supplementary submission.
Abbreviation: HCl, hydrogen chloride

8.7 Prescription Narcan Carton Design

Figure 15. Prescription Narcan Carton Design

Source: Miller (2018).

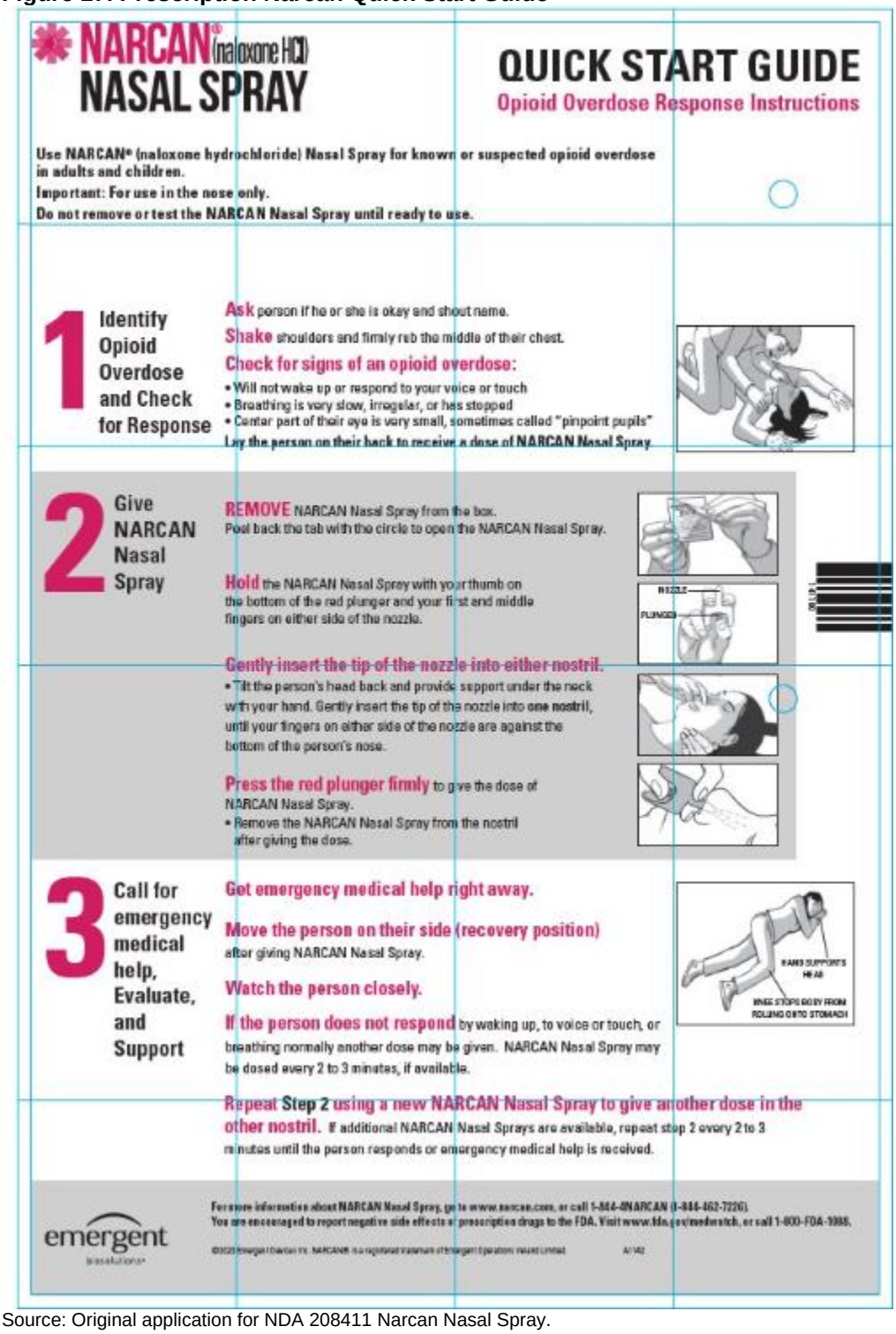
8.8 Prescription Narcan Blister Design

Figure 16. Prescription Narcan Blister Design With Quick Start Guide

Source: Daily Med.

8.9 Prescription Narcan Quick Start Guide (QSG)

Figure 17. Prescription Narcan Quick Start Guide



Source: Original application for NDA 208411 Narcan Nasal Spray.
Abbreviation: HCl, hydrogen chloride

8.10 Current Prescribing Information for Prescription Product

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*

*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 postapproval use of naloxone hydrochloride in the postoperative 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 postoperative 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.

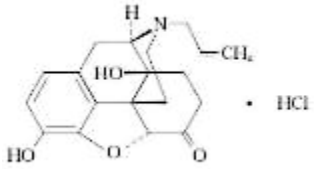
8.5 Geriatric Use

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 prefilled, single dose intranasal spray. Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one with the following structure:



C19H21NO4• 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 postdose. 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

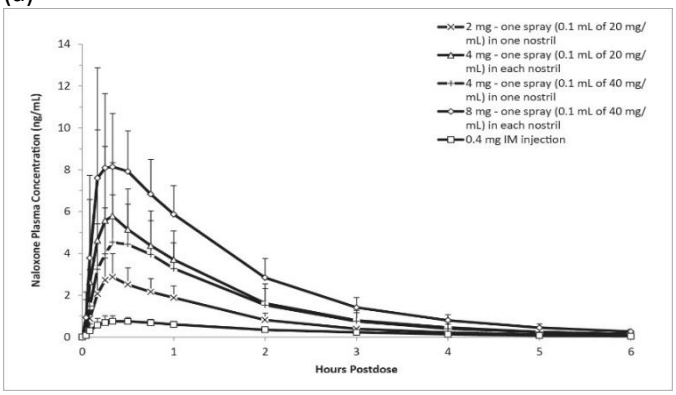
Parameter	2 mg– One Nasal Spray in one nostril 20 mg/ml (N=29)	4 mg – Two Nasal Sprays, one in each nostril 20 mg/ml (N=29)	4 mg – One Nasal Spray in one nostril 40 mg/ml (N=29)	8 mg – Two Nasal Sprays, one in each nostril 40 mg/ml (N=29)	0.4 mg Intramuscular Injection (N=29)
t_{max} (h)[†]	0.33 (0.25, 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)
$AUC_{0\text{-}inf}$ (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)

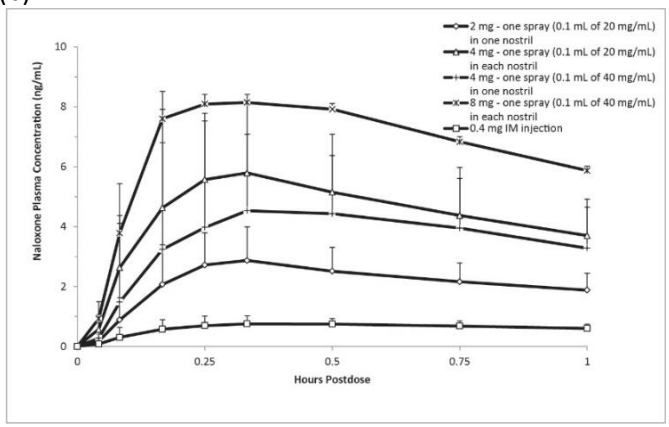
[††] N=28 for Relative BA.

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

(a)



(b)



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.

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.

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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:

- **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:
  - **body aches**
  - **diarrhea**
  - **increased heart rate**
  - **fever**
  - **runny nose**
  - **sneezing**
  - goose bumps
  - sweating
  - yawning
  - nausea or vomiting
  - **nervousness**
  - restlessness or irritability
  - shivering or trembling
  - stomach cramping
  - weakness
  - 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.narcanansalspray.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

8.11 Instructions for Use for Prescription Labeling

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.

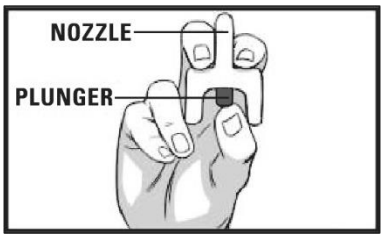
How to use NARCAN Nasal Spray:

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.

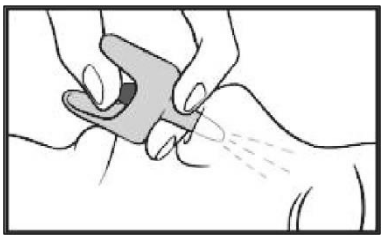
Note: NARCAN Nasal Spray freezes at temperatures below 5°F (-15°C). If this happens, the device will not spray. Get emergency medical help right away if this happens. Do not wait for NARCAN Nasal Spray to thaw. NARCAN Nasal Spray may still be used if it has been thawed after being previously frozen.

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.

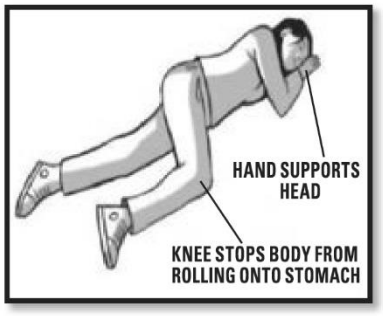


Step 6. Remove the NARCAN Nasal Spray from the nostril after giving the dose.

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).

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8.12 Clinical Opiate Withdrawal Scale

Figure 18. The Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Source: Wesson and Ling (2003).
Abbreviation: GI, gastrointestinal

8.13 Database Descriptions

FDA Adverse Event Reporting System

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

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

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

Drug Utilization Database Descriptions and Limitations

IQVIA NSP™

The IQVIA NSP™ measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and nonretail markets. It is the industry standard for measuring pharmaceutical spending because it captures ~89% of the total pharmaceutical market. Any capture of nonpharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage of over-the-counter products is generally less than 50%, though it may be higher for over-the-counter products with a National Drug Code number.

Sales volume is expressed in terms of sales dollars, reaches, extended units, and share of market. Outlets within the retail channel include chain drug stores, independent drug stores, mass merchandisers, and food stores. Outlets within the nonretail channel include clinics, nonfederal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Outlets within the mail channel are mail service pharmacies. NSP is used to monitor the actual volume amount of a product that is being distributed in any channel of the pharmaceutical marketplace. Except for the mail channel, these data are estimated based on national projections. Data are available in IQVIA's business intelligence tool SMART for 72 rolling months and are updated monthly.

Symphony Health Metys™

Powered by IDV® (Integrated Dataverse), Metys™ is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point. Metys™ accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning.

The dispensed prescriptions in the sample represent approximately 85% of all U.S. retail prescriptions; 73% of all U.S. mail-order prescriptions, and 75% of all U.S. specialty pharmacy prescriptions and 50% of all U.S. Long-Term Care pharmacy prescriptions. The retail, mail order, specialty and long-term care pharmacy prescriptions are projected to the national level. In addition, the database captures approximately 96% of pharmaceutical distribution into nonretail outlets in the United States. The nonretail data are not projected to the national level. Metys™ Managed Markets metrics, such as rejections and reversals are calculated using a 50% sample of pharmacy adjudicated claims projected to the national level.

8.14 HFVS Results (Qualitative Data Set)—Steps 2, 3, and 4

Table 14. HFVS Results (Qualitative Data Set)—Steps 2, 3, and 4

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

Information Supplied by Applicant

Total Number of Use Error (UE), Close Call (CC), Use Difficulty (UD): UE (n=5), CC (n=2), UD (n=9)

Use-Related Event	Participant Type, Literacy, and ID#	Applicant's RCA and Participants' Subjective Feedback (if Available)	Applicant's Discussion of Risk Mitigation Strategies
UE: Turned the manikin to the side, which blocked the moderator's view so it cannot be determined whether the participant completed the task correctly.	Adult Opioid User Associate NL # (b) (6)	Turned the manikin on its side thinking it would help keep the airway open.	Rated this use-related event as a use error conservatively because it could not be verified. No clinical consequence in an actual overdose emergency if the product was administered to a person in a lateral recumbent position.
UE: Did not keep the tip fully inserted up the nostril in the correct upwards orientation	Adult Opioid User NL # (b) (6)	Hand slipped slightly from the correct position into more of a posterior direction at the end of administration. "I used the thumb on the plunger. I'm not sure I understand what you want."	The tip of the device did not entirely exit the nostril, so in a real-world scenario the person would have likely still absorbed at least a partial dose through the nasal mucosa membrane. The participant properly administered a second dose, so no additional mitigation strategies were required.
UE: Squeezed the device without actually pushing in the plunger	Adolescent NL # (b) (6)	They held on to just the plunger and bottom of the device without stabilizing the top of the device with two fingers and was thus not able to put enough pressure to push the plunger. "Am I [inaudible] to get to squeeze? So, I kind of squeezed out instead of pushing it."	The moderator did not probe further to understand the participants' confusion and, therefore, there is not enough information to determine a root cause and/or mitigation strategy. Since this participant was the only one to experience this issue, further mitigation strategies are not required.

UE: Did not understand that she should actually administer the product in the demonstration	Adolescent NL # (b) (6)	Subjects were given minimal directions to preserve the naturalism of the demonstration. “I didn't really know if we were supposed to fully do it.”	This was a research artifact that would not be an issue in an actual overdose emergency, therefore no mitigation strategies were required.
UE: Held the device inverted, with the bottom of the plunger pointing up	Adolescent NL # (b) (6)	Subject did not understand the orientation of the device. Based on the subject’s behavior and feedback, the most likely root cause is that did not carefully review the pictogram associated with Step 2, and that the participant did not attempt to use the device, which may have cued him to his error. The participant assumed for unknown reasons likely that the device was not functional and thus he did not attempt to truly demonstrate, and thought that it was not a functional device. Additionally, the interviewer appears to have prematurely debriefed the participant on what they did wrong, after the HF demonstration but before the LC questions. Stated that the picture of the device on the DFL should be bigger or clarify direction “It just didn't say what direction to put it in.”	N/A, due to participant not fully engaging with the study and is considered an artifact of the research setting

CC: Participant did not depress plunger during initial attempt using the first device. Tried again after a delay and looking at the DFL and was able to press the plunger on a second attempt.	Adult Opioid User Associate LL #(b) (6)	Participant started reviewing the DFL at Step 3 and did not see the first panel before first attempt to administer the product. She seemed to know that she might not have done it correctly so referred to the DFL again, then attempted again after a brief delay using the first device and did push the plunger.	The order of the panels on the DFL was updated after the study so that Step 1 begins on the back of the box, which is more intuitive for consumers. No difficulty with second device/dose.
CC: Participant did not read Step 2c and press the plunger until 45 seconds after inserting the nozzle into the person's nostril.	Adult General Population LL #(b) (6)	Participant started reviewing the DFL at Step 3 and did not see the first panel before opening the blister pack for the first device and inserting into the nostril. Once he turned the carton to review Step 1, he administered with no difficulty. Participant later made a general statement that the color of the package was hard to see or that it was difficult to see where the steps were.	
UD: Participant inserted device into nostril, but then removed it, fumbled with it briefly, but then re-inserted and gave the dose. The participant then appeared to see if there was any more medicine in the device by attempting to administer again to the second nostril.	Adult Opioid User Associate NL #(b) (6)	Participant was acting nervous and excited and rushed to dispense the first dose. Additionally, the size of the nostrils of the manikin were just large enough to accommodate the tip of the nozzle.	Not provided
UD: Participant struggled to place tip of the nozzle in nostril and had to refer back to the instructions to confirm how to insert.	Adolescent NL #(b) (6)	Participant had her thumb on the plunger but did not stabilize the top of the device while inserting into the nostril, which caused the difficulty. Additionally, the nostrils of the manikin were just large enough to accommodate the tip of the device.	

UD: At first, the participant thought that the nozzle was a cap that was supposed to be removed before administering the dose.	Adult Opioid User LL # (b) (6)	Participant started reviewing the DFL at Step 3 and did not see the first panel before opening the blister pack for the first device. Once he turned the carton to see Step 1, he administered with no difficulty. "I was wondering if there was a cap on the end of that medication that had to be removed, and it doesn't say anything about the cap on here. So anyway, I just put the plunger in the nose, and then I inserted-- or pressed the back side of it, the nasal spray."	The order of the panels on the DFL was updated after the study so that Step 1 begins on the back of the box, which is more intuitive for consumers.
UD: Participant inserted the tip of the nozzle into the person's nostril and removed their hand, leaving the device in place for a moment while re-reviewing the directions to determine how to deliver a dose.	Adult General Population LL # (b) (6)	Participant reviewed the panel with Step 3 first, then realized something was not right as he was trying to follow the directions and administer. During this pause he left the device in the nostril. Once he reviewed Step 1, he administered the drug appropriately.	
UD: Brief struggle with plunger before administering the dose.	Adult Opioid User Associate NL # (b) (6)	Struggle with plunger seemed to be an artifact of also having the carton in her hand.	Not provided
UD: Participant used two hands to firmly press plunger. (n=2)	Adult Opioid User NL # (b) (6) Adolescent LL # (b) (6)	Participant may have been at an odd angle or may have perceived not having the hand strength needed to push the plunger using just one hand.	
UD: Participant hesitated to remove nozzle from person's nostril as if they were uncertain that the dose had been completely/fully given (n=2)	Adult General Population NL # (b) (6) Adult Opioid User LL # (b) (6)	Not provided	

Step 3: Call

- CALL 911 immediately after giving the 1st dose

Information Supplied by Applicant

Total Number of UE, CC, UD: UE (n=10), CC (n=5), UD (n=0)

Use-Related Event	**Use-Related Event**	**Use-Related Event**	**Use-Related Event**
UE: Verbalized calling 911 **prior to** giving the first dose	Adult Opioid User NL # (b) (6)	Verbally described calling 911, even though they did not simulate it. “I called 911 at the beginning before I gave the medication.”	Not provided
UE: Verbalized calling 911 after the first dose	Adult General Population LL # (b) (6)	RCA not provided “I was checking her airway first after I gave her the first dose.”	
UE: Called 911 **prior to** administering the first dose	Adult Opioid User Associate NL # (b) (6)	Did not read the directions far enough “I just didn't read them all.”	Calling 911 before administering the dose is not a critical error, since the 911 operator could help them through the process if needed and the victim would get the first dose of medicine very shortly thereafter.
	Adult Opioid User Associate NL # (b) (6)	Upon entering the simulation of a family member who is unconscious, some of these subjects acted out or described calling 911 before looking at the Narcan package, which would likely be common in any medical emergency of any kind. This type of error was not due to any fault of the device or labeling, participant was acting on instinct in an emergency. “Because I thought I already called them. I didn't think I needed to call them again.”	
	Adult General Population NL # (b) (6)		
	Adult Opioid User Associate NL # (b) (6)		
	Adolescent NL # (b) (6)		

	Adult Opioid User LL # (b) (6)	Looking at the back of the box (Panel 2 of the DFL) first, rather than Panel 1, which was on the side panel. “Because I didn't see it.” “I thought I did call 911 after the first dose-- or before the first dose. And then I waited the second two to three minutes for then to administer the second dose. I didn't know if I should be repeating the call, so.”	The DFL flow has been updated across the carton panels to be more intuitive and to better direct consumer attention to starting at Step 1, which is now on the back panel.
UE: Acted out in the simulation directing someone else to call 911 **prior to** giving first dose	Adult Opioid User Associate LL # (b) (6)	Assumed that there would be one other person there to call 911 while he attended to the unconscious family member. This was not due to any fault of the device or labeling; participant was acting on instinct in an emergency. “Because upon the first doses I thought that I had given, I had already screamed for somebody to call 911.”	Although not technically consistent with the label directions, directing a bystander to call 911 while the participant was orienting themselves to the label and how to administer the product is not a critical error and could expedite contacting emergency services.
UE: Verbally described calling 911 **prior to** giving first dose and then demonstrated /simulated calling 911 after the second dose	Adult Opioid User NL # (b) (6)	Participant actually did verbally state the need to call 911 after giving the first dose, but then actually acted out /simulated dialing after the second dose. It appears this was very conservatively scored and was not a true error. “I think that the steps should be bigger and bolder. I just feel like they need to be a little bit bigger than what the writing is next to it, kind of stand out a little bit bigger.”	The DFL flow has been updated across the carton panels to be more intuitive and to better direct consumer attention to starting at Step 1, which is now on the back panel.

CC: Participant called or described calling 911 **prior to** administering the first dose, but after reading the DFL, administered the first dose and called/stated they'd call 911 at that point or identified they'd still be on the phone with 911 (n=4)	Adult General Population NL #(b) (6) Adult Opioid User NL #(b) (6) Adult General Population NL #(b) (6) Adult General Population LL #(b) (6)	Participants started with the wrong side of the carton, which starts with Step 3 to call 911.	All participants quickly self-corrected after seeing the correct panel. The order of the panels on the DFL was updated after the study so that Step 1 begins on the back of the box, which is more intuitive for consumers.
CC: Participant did not call 911 until just less than 1 minute after the first dose	Adult General Population NL #(b) (6)	Participant spent about 50 seconds reading the wrong face of the DFL and was trying to determine how long to wait for the person to wake up before proceeding, before reading Step 3 to call 911.	It was a very brief delay and the first dose had been delivered successfully.

[26] The Applicant's IR response dated December 9, 2022 listed participant ID #(b) (6), which does not exist in the HF validation study report. Based on review of the participant transcripts, this appears to be participant ID #(b) (6).

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

Information Supplied by Applicant

Total Number of UE, CC, UD: UE (n=12), CC (n=0), UD (n=0)

Use-Related Event	Participant Type, Literacy and ID #	Applicant's RCA and Participants' Subjective Feedback (if Available)	Applicant's Discussion of Risk Mitigation Strategies
UE: Did not wait 2-3 minutes before administering a second dose or did not verbally describe the need to do so during the HF demonstration.	Adult Opioid User Associate NL # (b) (6)	Participants understood the need for a second dose if the person did not wake up but failed to time a 2-3-minute wait as part of their simulation or verbally articulate the need to wait 2-3 minutes. Upon review of the available participant comments, it appears that this was largely understood that the wait was assumed or implied, and that they didn't need to actually act out waiting for 2-3 minutes, i.e., an artifact of the research setting. "I was waiting. I figure the step three where you're calling 911, the duration of that would probably take you about two to three minutes. So I think it is pretty well placed. I figure someone would probably follow that step immediately after making that call to 911. But since, obviously, it's not a real phone, I put it down and decided to wait maybe like 60 seconds before moving on."	The act of calling 911 for emergency services after administering the first dose would result in some delay between doses in a real-life setting if a consumer failed to notice or understand this direction. While the label instructs a User to wait 2-3 minutes before delivering a 2nd dose, administering one sooner is not considered a critical use error.
	Adolescent NL # (b) (6)		
	Adult Opioid User NL # (b) (6)		
	Adult Opioid User Associate NL # (b) (6)		
	Adult Opioid User NL # (b) (6)		
	Adolescent NL # (b) (6)		
	Adult General Population NL # (b) (6)		
	Adolescent LL # (b) (6)	"I kind of just went with it as imagining it was two or three minutes."	

	Adolescent NL # (b) (6)	"I didn't even think about that. I guess just because you said to move on that I just assumed I waited two to three minutes."	
	Adult Opioid User Associate LL # (b) (6)	"Just missed a step. I figured wait for 911 to come. That's why I kept listening. If there were two, three minutes of-- I guess. I got lost in it."	
UE: Did not administer or discuss need to administer a second dose	Adolescent LL # (b) (6)	This participant somewhat modified the scenario provided to them by including in their demonstration a statement that emergency personnel had arrived shortly after giving the first dose, and she stated that in her "scenario," the person would be waking up. However, this participant also did not provide a correct answer to the associated LC question, responding with "It says to check with them again, but make sure you call 911." "Because my patient or family member [laughter] was waking up. So I didn't feel that they needed the second dose."	Not provided

UE: Failed to administer a second dose	Opioid User Associate LL #(b) (6)	She set down the box after administering the first dose and did not appear to finish reading all directions during the HF demonstration – she appeared to have gotten upset thinking about it being a real-life scenario and focused on all other additional lifesaving measures she could try in addition to Narcan rather than referring to all Steps on the package during the HF demonstration. "Just try to resuscitate him and do this. Try to get him to breathe again through mouth-to-mouth or CPR. That's all I can [inaudible] to do. Wait for the ambulance to get there."	This subject failed to demonstrate or verbalize the need to administer a second dose during the HF demonstration but did demonstrate clear understanding of this concept in the LC question by responding to give Narcan twice "Administer the Narcan. Put it in the nose. Spray it one time, it says. Then call 911. Check to make sure they're breathing. [inaudible] check to make sure they're breathing and administer the Narcan" and then later: "Call 911 and then proceed to give them a dose every two to three minutes" as well as "I don't know. I'd say that maybe I could do another dose. Yeah. Give another dose of it." Therefore, no additional mitigation strategies were required.

Source: Collated and compiled by FDA from the Applicant's submission and responses to information requests.
Abbreviations: CC, close call; CPR, cardiopulmonary resuscitation; DFL, Drug Facts Label; HF, human factors; ID, identifier; LC, label comprehension; LL, limited literacy; NL, normal literacy; RCA, root cause analysis; UD, use difficulty; UE, use error