

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208411Orig1s006

INTEGRATED REVIEW

Integrated Review**Table 1. Administrative Application Information**

Category	Application Information
Application type	NDA
Application number(s)	208411/S-006
Priority or standard	Priority
Submit date(s)	9/29/2022
Received date(s)	9/29/2022
PDUFA goal date	3/29/2023
Division/office	Division of Non-Prescription Drugs I (DNPDI)
Review completion date	3/29/2023
Established/proper name	Narcan (naloxone hydrochloride) nasal spray, 4 mg
(Proposed) proprietary name	Narcan NS
Pharmacologic class	Opioid antagonist
Code name	Not applicable
Applicant	Emergent BioSolutions Inc.
Dosage form(s)/formulation(s)	Intranasal (IN) Spray
Dosing regimen	Give 1st dose; if the person does not wake up, continue to give doses every 2-3 minutes until the person wakes up
Applicant proposed indication(s)/ population(s)	To revive someone during an overdose from many prescription pain medications or street drugs such as heroin
Proposed SNOMED indication	724653003 Opioid dependence with current use (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	4 mg
Approved indication(s)/ population(s) (if applicable)	As above
Approved SNOMED term for indication (if applicable)	As above

Table of Contents

Table of Tables	viii
Table of Figures	ix
Glossary	1
I. Executive Summary.....	3
1. Summary of Regulatory Action	3
2. Benefit-Risk Assessment.....	5
2.1. Benefit-Risk Framework	5
2.2. Conclusions Regarding Benefit-Risk	9
II. Interdisciplinary Assessment.....	11
3. Introduction	11
3.1. Review Issue List.....	13
3.1.1. Key Efficacy Review Issues.....	13
3.1.1.1. Efficacy of NNS Is Well Established as a Prescription Product for the Treatment of Opioid Overdose for All Ages, Including Neonates	13
3.1.1.2. Drug Facts Label and Pictograms Tested Well for Comprehension by Consumers	13
3.1.1.3. Availability of Nonprescription NNS Has the Potential to Address Barriers and Increase Naloxone Access to Consumers	13
3.1.2. Key Safety Review Issues.....	13
3.1.2.1. Naloxone-Induced Precipitated Withdrawal	13
3.1.2.2. Limited Efficacy	13
3.1.2.3. Device Use Errors and Additional Medication Errors	13
3.1.2.4. Limitations of Human Factors Validation Study Methodology	13
3.1.2.4.1. Pediatric Users Less Than 15 Years of Age Were Not Included in the HFVS.....	13
3.1.2.4.2. Two User Groups Did Not Include at Least 30% Limited Literacy Participants.....	13
3.1.2.4.3. Participants Were Allowed an Unlimited Familiarization Period.....	13
3.1.2.4.4. Moderators Employed Use of Leading Language and the “Think Aloud” Method.....	13
3.1.2.4.5. Mock Carton Labeling Tested in the HFVS Differs From the Intend-to-Market Carton Labeling	14
3.1.2.5. Qualitative Human Factors Validation Study Findings.....	14
3.1.2.5.1. Directions of the DFL Spanned Across the Back and Side Panels and Contributed to Use Errors, Close Calls, and Use Difficulties.....	14

3.1.2.5.2. Proposed User Interface Lacks Adequate Depiction of Correct Hand and Finger Positioning	14
3.1.2.5.3. Proposed DFL Directions on Nozzle Insertion Contributed to a Use Error.....	14
3.1.2.5.4. Proposed Labeling Does Not Adequately Communicate the Number of Doses Per Nasal Spray Device	14
3.2. Approach to the Clinical Review.....	14
4. Patient Experience Data	16
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology	16
5.1. Nonclinical Assessment of Potential Effectiveness.....	16
5.2. Clinical Pharmacology/Pharmacokinetics	17
6. Efficacy (Evaluation of Benefit)	17
6.1. Assessment of Dose and Potential Effectiveness	17
6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy	17
6.3. Key Efficacy Review Issues	17
6.3.1. Efficacy of NNS Is Well Established as a Prescription Product for the Treatment of Opioid Overdose for All Ages, Including Neonates	17
6.3.2. Drug Facts Label and Pictograms Tested Well for Comprehension by Consumers	20
6.3.3. Availability of Nonprescription NNS Has the Potential to Address Barriers and Increase Naloxone Access to Consumers	27
7. Safety (Risk and Risk Management).....	29
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data.....	29
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug- Specific Factors	29
7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience	29
7.4. FDA Approach to the Safety Review	30
7.5. Adequacy of the Clinical Safety Database	31
7.6. Safety Results	31
7.6.1. Postmarket Safety Evaluation From the Applicant's Pharmacovigilance Database	32
7.6.2. Published Literature	39
7.7. Key Safety Review Issues	41
7.7.1. Naloxone-Induced Precipitated Withdrawal	41
7.7.2. Limited Efficacy.....	43
7.7.3. Device Use Errors and Additional Medication Errors	44
7.7.4. Limitations of Human Factors Validation Study Methodology.....	47

7.7.4.1. Pediatric Users Less Than 15 Years of Age Were Not Included in the HFVS	47
7.7.4.2. Two User Groups Did Not Include at Least 30% Limited Literacy Participants	47
7.7.4.3. Participants Were Allowed an Unlimited Familiarization Period	48
7.7.4.4. Moderators Employed Use of Leading Language and the “Think Aloud” Method	48
7.7.4.5. Mock Carton Labeling Tested in the HFVS Differs From the Intend-to-Market Carton Labeling	49
7.7.5. Qualitative Human Factors Validation Study Findings	51
7.7.5.1. Directions of the DFL Span Across the Back and Side Panels Contributed to Use Errors, Close Calls, and Use Difficulties	51
7.7.5.2. Proposed User Interface Lacks an Adequate Depiction of Correct Hand and Finger Positioning	52
7.7.5.3. Proposed DFL Directions on Nozzle Insertion Contributed to a Use Error	54
7.7.5.4. Proposed Labeling Does Not Adequately Communicate the Number of Doses Per Nasal Spray Device	54
8. Therapeutic Individualization	55
8.1. Intrinsic Factors	55
8.2. Extrinsic Factors	55
8.3. Plans for Pediatric Drug Development	55
8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential	55
9. Product Quality	55
9.1. Device or Combination Product Considerations	55
9.2. Summary	56
9.3. Drug	56
9.4. Drug Formulation	56
9.5. Relevant Regulatory History	57
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review	61
11. Advisory Committee Summary	61
III. Additional Analyses and Information	63
12. Summary of Regulatory History	63
12.1. Efforts to Increase Access to Naloxone	63
12.2. Development of Nonprescription NNS	64
12.3. Development of the Human Factors Program	65
12.4. Pediatric Assessment	66
13. Pharmacology Toxicology	67

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application	67
13.2. Individual Reviews of Studies Submitted With the New Drug Application	67
13.3. Executive Summary	67
13.3.1. Introduction	67
13.3.2. Brief Discussion of Nonclinical Findings	68
13.3.3. Recommendations	68
13.3.4. Additional Nonclinical Recommendations	68
13.3.5. Labeling	68
13.4. Drug Information	68
13.4.1. Drug	68
13.4.2. Relevant INDs, NDAs, BLAs and DMFs	69
13.5. Drug Formulation	69
13.5.1. Comments on Novel Excipients	70
13.5.2. Comments on Impurities/Degradants of Concern	71
13.5.3. Proposed Clinical Population and Dosing Regimen	71
13.5.4. Regulatory Background	71
13.6. Studies Submitted	72
13.6.1. Studies Reviewed	72
13.6.2. Studies Not Reviewed	73
13.6.3. Previous Reviews Referenced	73
13.7. Pharmacology	73
13.7.1. Primary Pharmacology	73
13.7.2. Secondary Pharmacology	74
13.7.3. Safety Pharmacology	74
13.8. Pharmacokinetics/ADME/Toxicokinetics	75
13.8.1. PK/ADME	75
13.8.2. Toxicokinetics	75
13.9. General Toxicology	76
13.10. Genetic Toxicology	76
13.11. Carcinogenicity	76
13.12. Reproductive and Developmental Toxicology	76
13.13. Integrated Summary and Safety Evaluation	77
14. Clinical Pharmacology	78
14.1. In Vitro Studies	78
14.2. In Vivo Studies	78
14.3. Bioanalytical Method Validation and Performance	79
14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety	79

14.5. Pharmacometrics Assessment.....	79
14.6. Pharmacogenetics	79
15. Study/Trial Design	79
16. Efficacy	79
17. Clinical Safety	79
17.1. Review of the Applicant's Assessment of FAERS.....	79
17.1.1. Limitations	79
17.1.2. General Findings	80
17.1.3. Serious Outcomes by Intranasal Route of Administration.....	81
17.1.4. Serious Outcomes by Age and Intranasal Route of Administration	82
17.1.5. Deaths.....	83
17.1.6. Safety Topics of Interest	84
17.1.6.1. Use Error	84
17.1.6.2. Product Ineffective	84
17.1.6.3. Drug Allergy and Hypersensitivity	85
17.1.6.4. Opioid Withdrawal	85
17.2. Review of the Applicant's Assessment WHO Vigibase.....	86
17.2.1. General Findings	86
17.2.2. Serious Outcomes	87
17.2.3. Safety Topics of Interest	87
17.2.3.1. Use Error	87
17.2.3.2. Product Ineffective	88
17.2.3.3. Drug Allergy and Hypersensitivity	88
17.2.3.4. Naloxone-Induced Precipitated Withdrawal	88
18. Clinical Virology.....	89
19. Clinical Microbiology	89
20. Mechanism of Action/Drug Resistance.....	89
21. Other Drug Development Considerations	90
22. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections).....	90
23. Labeling: Key Changes and Considerations	90
23.1. Approved Labeling Types	90
23.2. Approach to the Labeling Review	90
23.3. Review Issues	91
23.4. Assessment	92
23.4.1. Drug Facts Label.....	92
23.4.2. Principal Display Panel.....	96
23.4.3. Blister Pack Labeling	97

23.4.4. Nasal Spray Device Labeling	98
23.4.5. Outstanding Items to Address During Label Negotiations	98
24. Postmarketing Requirements and Commitments	100
25. Financial Disclosure	100
26. References	100
27. Review Team.....	103
27.1. Reviewer Signatures	105

Table of Tables

Table 1. Administrative Application Information	i
Table 2. Benefit-Risk Framework.....	5
Table 3. Currently Approved Single-Ingredient Naloxone Products*.....	12
Table 4. Patient Experience Data Submitted or Considered.....	16
Table 5. Comparison of Mean Naloxone Concentrations From 2.5 to 60 Minutes Postdose	19
Table 6. Demographics of the Study Population	22
Table 7. Pivotal Label Comprehension Study Primary and Secondary Endpoints.....	24
Table 8. Results for the Label Comprehension Study Primary Endpoints	25
Table 9. Results for the Label Comprehension Study Secondary Endpoints	26
Table 10. Preferred Terms Appearing >1% Among Cases Reporting Serious Outcomes	33
Table 11. Relevant INDs and NDAs.....	69
Table 12. Relevant DMFs	69
Table 13. Quantitative Composition of the Nonprescription Formulation	70
Table 14. Quantitative Composition of the Prescription Formulation.....	70
Table 15. Sources of Pharmacological and Toxicological Information Reviewed	73
Table 16. Previous Reviews Referenced	73
Table 17. Baseline Patient Characteristics and Route of Administration by Serious and Nonserious Outcomes	81
Table 18. Most Frequently Reported Preferred Terms (>1%) for All Serious Cases Associated with Intranasal Route of Administration	81
Table 19. Preferred Terms Reported with >1% Difference in the Elderly Versus General Adults in Serious Cases Involving Intranasal Naloxone	83
Table 20. Fatal Outcomes by Route of Administration	83
Table 21. Potential Opioid Withdrawal Cases by Route of Administration in FAERS	85
Table 22. Most Frequently Reported Preferred Terms (>1%) From All Serious Cases....	87
Table 23. Proposed Draft Labeling.....	91
Table 24. Reviewers of Integrated Assessment (Digital Signatures in Table 26 Listed in Same Order).....	103
Table 25. Additional Reviewers of Application/Advisory Committee (Digital Signatures Not Required).....	104
Table 26. Signatures of Reviewers	105

Table of Figures

Figure 1. Mean Plasma Concentration-Time Profiles of Naloxone (IN and IM) From 0 to 4 Hours.....	18
Figure 2. FDA’s Model Naloxone Drug Product DFLs for Use With Either a Nasal Spray or Autoinjector (Respectively)	21
Figure 3. Applicant’s Proposed Nonprescription Narcan (Naloxone Hydrochloride) Nasal Spray, 4 mg DFL and Associated Labeling for NDA 208411/S-006	27
Figure 4. Mock Carton Tested in the HFVS Versus Intend-to-Market Carton Submitted	50
Figure 5. Mock Carton PDP Tested in the HFVS Versus Intend-to-Market Carton PDP Submitted September 29, 2022.....	51
Figure 6. Prescription NNS Pictograms.....	53
Figure 7. Nonprescription NNS DFL Step 2 Pictogram	53
Figure 8. Structure or Biochemical Description	69
Figure 9. Change (b) (4) for the 4 mg Presentation ...	72
Figure 10. Diagram of the Narcan (Naloxone HCl) Nasal Spray With Device Components (Not to Scale).....	78
Figure 11. FDA Model Drug Facts Label.....	93
Figure 12. Proposed Narcan Drug Facts Label	95
Figure 13. Proposed PDP	97
Figure 14. Proposed Blister Pack Label.....	98
Figure 15. Proposed Nasal Spray Device Labeling	98

Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ARGUS	Applicant's pharmacovigilance database
AUC	area under the concentration-time curve
CCS	container closure system
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CONFER	Comprehension for OTC Naloxone (pivotal label comprehension study)
COWS	Clinical Opiate Withdrawal Scale
CR	Complete Response
CV	coefficient of variation
DFL	drug facts label
DMF	drug master file
EDTA	disodium edetate
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FR	Federal Register
GEN2	new formulation of naloxone
HCl	hydrochloride
HF	human factors
HFVS	human factors validation study
IFU	instructions for use
IM	intramuscular(ly)
IN	intranasal
IND	investigational new drug
INN	intranasal naloxone
IV	intravenous(ly)
LB	lower bound
LL	limited literacy
LCS	label comprehension study
MedDRA	Medical Dictionary for Regulatory Activities
NAL	naloxone access laws
NDA	new drug application
NL	normal literacy
NNS	Narcan nasal spray
nonRx	nonprescription
NPD-PTS	Nonprescription Drug Pharmacology Toxicology Staff
OSE	Office of Surveillance and Epidemiology
OTC	over-the-counter
PDP	principal display panel
PE	point estimate

NDA 208411/S-006

Narcan (naloxone hydrochloride) nasal spray, 4 mg

PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PT	preferred term
P/T	pharmacology toxicology
QSG	quick start guide
REALM	Rapid Estimate of Adult Literacy in Medicine
RH	relative humidity
Rx	prescription
SC	subcutaneous(ly)
SD	standard deviation
SOC	system organ class
UE	use error
WHO	World Health Organization

I. Executive Summary

1. Summary of Regulatory Action

Emergent BioSolutions Inc. (hereinafter referred to as the Applicant) submitted a supplementary new drug application (sNDA 208411/S-006) for Narcan (naloxone hydrochloride) 4 mg nasal spray on September 29, 2022, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.71. The Applicant requests a complete switch of its 4 mg naloxone nasal spray product from prescription (Rx) to nonprescription status. Narcan nasal spray (NNS) is a single-use, fixed-dose, drug-device combination product approved 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.” NNS is approved for community use. A community use treatment may be administered by individuals without medical training (i.e., laypeople) in community settings without the need for additional supplies or assembly before use.

Currently, there are no approved nonprescription naloxone products. Prescription naloxone products, including NNS, are frequently administered using a variety of community-based naloxone distribution programs and without a patient-specific prescription under state naloxone access laws (NAL). However, despite implementation of state NALs, opioid overdose deaths have continued to climb. Stakeholders report that access to naloxone via state NALs has been hindered by a lack of pharmacy participation in stocking and distributing naloxone products, stigma faced by consumers purchasing naloxone at pharmacies, and difficulties faced by harm reduction groups in accessing bulk purchases of naloxone due to its prescription status ([Evoy et al. 2021](#); [Green et al. 2017](#); [Tsai et al. 2019](#)). The availability of a nonprescription naloxone product is anticipated to address some of these obstacles to broader naloxone access and thereby help combat the opioid crisis.

While the models of community-based naloxone distribution and NALs help to inform the potential public health benefit of nonprescription naloxone, they do not necessarily inform us on whether a layperson could, on their own, safely, and effectively administer NNS without the supervision of a healthcare provider by relying only on the labeling (87 FR 68702, November 16, 2022). 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. In addition to the instructions that providers give when writing a prescription, under state NALs and collaborative agreements pharmacists may also offer instruction to those purchasing naloxone. Thus, prescription status is not the same as nonprescription status where a product may be purchased without any additional instruction other than the carton and container.

For its nonprescription product, the Applicant seeks the indication “to revive someone during an overdose from many prescription pain medications or street drugs such as heroin.” The Applicant intends for the dosing instructions of the nonprescription product to be the same as for the prescription product - one spray intranasally into one nostril, administering additional doses using a new nasal spray every two to three minutes until the person wakes up. The

nonprescription product is intended for use in all ages, from neonate to adult, just like the prescription product.

This sNDA contained a limited amount of new information that was not previously submitted or reviewed in the original prescription application approved on November 18, 2015. In the current application, the Applicant provided no new nonclinical data or clinical trials containing efficacy and safety data. No formulation changes or significant manufacturing changes were proposed for the product. The drug product (drug and device) being proposed for nonprescription use is unchanged from the currently approved product. The main changes made to the product and contained in this application were packaging and labeling changes, including that of the carton, blister pack, and package inserts.

To support nonprescription use of this product, the Applicant utilized FDA's model naloxone drug facts label (DFL), which was tested and validated by FDA in a pivotal label comprehension study conducted among a wide range of potential nonprescription naloxone users (84 FR 8728, March 11, 2019). Product-specific information was added to the DFL. The Applicant conducted a human factors validation study (HFVS) to demonstrate that the new user interface (including the product, its packaging, and labeling) can be used safely and effectively among groups of potential nonprescription users. The study was performed by the Applicant without input from FDA regarding trial design and conduct. In addition, the Applicant presented five years of routine pharmacovigilance data with summaries from its own postmarketing safety database as well as external databases and a comprehensive review of the published literature.

This application was granted priority review status reflecting the importance of this product from the public health perspective. The application was also discussed at a joint meeting of the Nonprescription Drugs Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee on February 15, 2023, as it represents a potential first-in-class product in a new therapeutic category for nonprescription drugs. Members of the joint committees unanimously voted for approval of NNS for nonprescription use. They did make some recommendations for labeling changes to improve the usability of the nonprescription product.

The application was reviewed by a multidisciplinary review team consisting of members from the Division of Nonprescription Drugs I, Division of Anesthesiology, Addiction Medicine, and Pain Medicine, the Division of Medication Error Prevention and Analysis, the Division of Pediatric and Maternal Health, the Office of Pharmaceutical Quality, and Nonprescription Drugs Pharmacology and Toxicology Staff (NPD-PTS). In addition, the Office of Surveillance and Epidemiology was consulted to provide FDA's independent review of drug utilization and postmarketing safety data.

Each discipline has recommended approval of the proposed nonprescription product. The overall benefit-risk assessment is favorable as described in [Table 2](#). For complete information supporting the basis for this approval, please refer to the detailed reviews included in this Interdisciplinary Assessment document.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Opioid overdose is characterized by potentially life-threatening respiratory and central nervous system depression. - Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and/or prescription opioids has been steadily rising in the United States for more than a decade. - In 2017, the U.S. Department of Health and Human Services declared the opioid crisis a public health emergency and has renewed the declaration multiple times since the initial declaration (Administration for Strategic Preparedness & Response 2022). - More than 80,000 people died of opioid-involved overdose deaths in 2021 (Ahmad et al. 2023).	Opioid overdose is a serious condition and continuously rising numbers of opioid overdose deaths is a public health emergency in the United States.
Current Treatment Options	- Naloxone is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites. It reverses the effects of opioids, including respiratory depression, sedation, and hypotension. - Naloxone has been approved since 1971. - Naloxone is available in several strengths, dosage forms, and presentations including several naloxone products that were designed for “community use.” These community use products can be administered by individuals without medical training [laypeople] because they do not require additional supplies or assembly prior to use. - At the present time, all naloxone products are prescription products.	Naloxone is a critical tool to help reduce opioid overdose deaths and address this public health crisis. Current naloxone access pathways appear to be inadequate at making naloxone easily accessible. Approval of a nonprescription naloxone product may address some of the current barriers to access naloxone and broaden availability to this life-saving therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- All 50 states and the District of Columbia have passed NALs to expand layperson access to naloxone. Each state has different provisions. Many feature provisions that allow for nonpatient specific prescriptions or allow a prescriber to prescribe naloxone to someone not directly at risk of overdose, and provide civil and criminal liability immunity to laypeople who administer naloxone in good faith to someone believed to be experiencing an opioid-related overdose (Legislative Analysis and Public Policy Association 2023) - Many pharmacists also provide naloxone to patients using naloxone collaborative practice agreements. - Barriers to accessing naloxone continue to exist, including lack of uniform pharmacy participation in naloxone distribution (Correal 2018; Meyerson et al. 2018), stigmatization of consumers who try to access naloxone, the need for interaction with a pharmacist to obtain prescription naloxone (Evoy et al. 2021), and inaccessibility of bulk purchasing of naloxone by harm reduction groups (Lloyd 2018). - Nalmefene hydrochloride is an alternative prescription opioid antagonist with a longer duration of action than naloxone. Nalmefene is available for intravenous, intramuscular, and subcutaneous administration. It is primarily used in hospital settings.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	- The efficacy of NNS to reverse the effects of opioids was established with its 2015 approval; its general efficacy for this indication is not in question. - Further evidence for the effectiveness of intranasal naloxone is supported by the small number of postmarketing reports of “limited efficacy” among cases reporting intranasal naloxone use in the community setting. - Postmarketing distribution information shows that intranasal naloxone is in high distribution and comprises the majority of dispensed prescription naloxone see Office of Surveillance and Epidemiology (OSE) Consult Review dated February 27, 2023 (DARRTS Reference ID: 5131876). The Applicant reported a cumulative distribution of (b) (4) doses between February 2016 through June 2021. - In a pivotal label comprehension study, general consumers and opioid users demonstrated adequate comprehension of critical labeling information using the FDA model naloxone DFL. Individuals with limited literacy and adolescents also performed adequately.	NNS is effective for the emergency treatment of known or suspected opioid overdose. NNS is expected to be effective as a nonprescription product as supported by findings of the pivotal label comprehension study; and the previously collected postmarketing safety data for the product when used in the community.
Risk and Risk Management	- Naloxone has a well-established safety profile with a wide safety margin that is supported by over 50 years of postmarketing experience. - In the postmarketing safety data, there were generally few reported cases of serious adverse events such as naloxone-induced precipitated withdrawal, pulmonary edema, seizures, and device use errors associated with intranasal naloxone use. Few serious adverse events were found among pediatric patients, geriatric patients, or pregnant women. Adverse events were consistent with naloxone’s known adverse event profile. - The most frequently reported preferred terms among serious cases were not unexpected considering the condition being treated.	There were no new or unexpected safety findings in the postmarketing safety data. Adverse events reported were generally consistent with the condition being reported or a known side effect for naloxone. Potential adverse events from naloxone or from use of naloxone to treat a nonopioid condition may be mitigated by the directions to “Call 911” as part of product administration. The Applicant has agreed to alter the placement of the IFU and keep all five steps together on the back panel of the carton to address use errors. Although the picture showing hand placement on the nasal spray device was less than ideal, the Applicant has agreed to modify its pictograms. A better pictogram depicting hand placement may positively impact successful use of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The HFVS demonstrated use errors related to the positioning of IFU on several panels of the carton leading to some users reading the IFU out of sequence. • The HFVS demonstrated use errors related to hand positioning on the device and placement in nostril. • The initial application did not include a Quick Start Guide. This meant that if the drug product was separated from the carton, the consumer would not have instructions readily available. • The safety findings and HFVS suggest that users were not always aware that the nasal spray contained just a single dose nor were they always aware that the device does not need to be primed. • The HFVS suggests that users might have confusion that the nasal spray device is only intended to be administered in the nose and that the nozzle needs to be fully inserted.	Additionally, the components of the device (the nozzle and the plunger) will be labeled. The Applicant has also agreed to include a Quick Start Guide inside each blister package of product. The label will contain information to state that each container contains two nasal sprays, and the nasal spray should not be primed as the nasal spray only contains one dose. The label will contain information that the nasal spray is intended for placement in the nose and the nozzle needs to be inserted in the nose for effective use.

Abbreviations: DFL, Drug Facts Label; HFVS, human factors validation study; IFU, instructions for use; NALs, naloxone access laws; NNS, Narcan nasal spray

2.2. Conclusions Regarding Benefit-Risk

The benefit-risk profile and modified consumer labeling adequately support the switch of NNS 4 mg, an opioid receptor antagonist, from prescription to nonprescription status. The indication is for the emergency treatment of opioid overdose, to revive someone during an overdose from many prescription pain medications or street drugs such as heroin. The medication can save a life. NNS 4 mg is indicated for all ages from neonate to adult. It is sprayed in the nostril. After checking to see if the individual has not responded, the dose can be repeated every two to three minutes until emergency help arrives. Consumer testing supports that bystanders can accomplish this without any help other than the instructions for use.

Between February 2016 to June 2021, the Applicant indicates they have distributed approximately (b) (4) units of NNS and relatively few serious adverse event reports have been filed. Although this may be in part because some are being treated for overdose of illicit substances and may be less willing to report adverse events (AEs), it is still remarkable how few AE reports have been filed given the known distribution of the product. For those who do not have opioids on board, naloxone has no effect; the risks of inadequate treatment of another serious condition are mitigated by the “Call 911” instruction for use. For those who do have an opioid overdose, serious AEs may occur when treated with naloxone. However, the AEs are infrequent and unpleasant, though not generally life-threatening. Many of the AEs reported are characteristic of the underlying condition such as opioid withdrawal symptoms and are manageable if consumers follow the instructions and call 911 for further emergency help after the initial symptoms of overdose are treated. If opioid overdose is untreated, it generally leads to death or severe morbidity such as cerebral hypoxia.

Opioid overdose has been an increasing problem in the United States for the last two decades since the Centers for Disease Control and Prevention began collecting data. More than a million people have died from drug overdose, largely caused by opioids, but the greatest rise has been in the last few years, predominantly because of the influx of highly potent synthetic opioids into this country. Deaths from opioid overdose account for 90% of the overdoses in the United States and opioid overdose rose from 69,061 in 2020 to 80,926 in 2021, a rise of 17.2% in 1 year ([Ahmad et al. 2023](#)). Deaths occur most frequently in those ages 18 to 65 years but occur in all ages, including children, especially those ages 15 to 19 years. Opioid overdose can occur in a patient prescribed an opioid medication, in household contacts of patients using opioids, in people who obtain opioids illegally, and in those who take opioids unknowingly, such as from a poisoning from counterfeit and illicit medications ([Kuehn 2023](#)). As previously stated, 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.

At the present time, all naloxone products are available by prescription. NNS is distinguished from injectable products as it is available for community use. That is, it can be administered by individuals without medical training and without additional supplies or assembly prior to use. Some believe that the prescription status of naloxone has presented a barrier to the wider access of naloxone. Although all 50 states have naloxone access laws to expand access, state laws may have different provisions, and this can make it more confusing or cumbersome for pharmacists. Many feature provisions that allow for nonpatient-specific prescriptions to individuals or bulk

orders to harm reduction groups or for someone to purchase naloxone who is not directly at risk of overdose. Despite these laws, access is not always readily or easily available. Additionally, the lack of uniform pharmacy participation in naloxone distribution, stigmatization of consumers who try to access naloxone, the need for interaction with a pharmacist to obtain prescription naloxone ([Evoy et al. 2021](#)), and inaccessibility of bulk purchasing of naloxone by harm reduction groups all hamper the easy distribution of naloxone in the community. Nonprescription status is expected to improve the ease of access.

The evidence that was required to switch NNS from prescription to nonprescription status included a review of the postmarketing safety results since the time that the nasal spray product was initially marketed for community use, a review of the DFL and the associated FDA validated label comprehension study, and a review of the human factors validation study (HFVS) performed by the Applicant. In the postmarketing safety data, it was noted that there were relatively few serious adverse events reported including in pediatric, geriatric, and pregnant users of the product. The most frequent AEs were consistent with naloxone's known AE profile and were generally recoverable. In the FDA pivotal label comprehension study, consumers, both those of normal and limited literacy (LL), performed well, comprehending critical labeling information from the DFL. This was also the case for adolescents ages 15 years and above.

Although the HFVS generally demonstrated that consumers could use the product, the design of the study was less than ideal and several use errors occurred, suggesting that packaging/labeling could be significantly improved. For example, the blister packs did not contain quick start guides. The containers did not have the instructions for use (IFU) all on one side of the carton, and individuals sometimes started with Step 3 of the DFL rather than Step 1. The pictograms showing the placement of the hand on the device with the nozzle tip in the nose were confusing and led to some use errors. Some users were unaware that the device did not need to be primed and could only be used once or that the nozzle needed to be fully inserted in the nose.

Additionally, the study was not done with time constraints and participants were talked through the study, which is not replicative of a real-life circumstance. Based on these use errors, the Applicant agreed to make modifications to further optimize the product's user interface and labeling materials. The conclusion of the recent Advisory Committee was 19/0 in favor of approving NNS with label modifications as a nonprescription product and to not require additional human factors testing, despite the flaws of the HFVS. This is fitting given the benefit-risk ratio of saving a life with the product.

II. Interdisciplinary Assessment

3. Introduction

Naloxone is a nonselective opioid receptor antagonist that reverses the effects of respiratory depression and sedation by displacing opioids from the mu-opioid receptor in the central nervous system. Timely administration of naloxone during an opioid overdose can reverse life-threatening effects of the overdose, prevent hypoxia-associated injury, and death. Naloxone was first approved in the United States in 1971 under new drug application (NDA) 016636 as an injection product that could be administered subcutaneously (SC), intramuscularly (IM), or intravenously (IV).

Narcan nasal spray (NNS) 4 mg was approved under the current NDA on November 18, 2015, as the first approved nasal spray formulation of naloxone. NNS is a single-use, fixed-dose, drug-device combination product that is intended for community use. The Applicant proposes a complete switch of NNS from prescription to nonprescription marketing.

Therapeutic Context

Analysis of Condition

Opioid overdose is a serious condition that is characterized by potentially life-threatening respiratory and central nervous system depression. Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and/or prescription opioids is a public health crisis in the United States. Opioid overdose can occur in a patient prescribed an opioid medication or in household contacts of the patient and in people who misuse or abuse opioids.

The number of opioid overdose deaths per year has been steadily rising in the United States for more than a decade. The number of opioid overdose deaths per year in 2015 was 33,203 which increased to 69,061 in 2020 and as high as 80,997 by the end of 2021 ([Ahmad et al. 2023](#)). In 2017, the U.S. Department of Health and Human Services declared the opioid crisis a public health emergency and has renewed the declaration multiple times since the initial declaration ([Administration for Strategic Preparedness & Response 2022](#)). Health and Human Services has made addressing this public health crisis a top priority and has outlined a targeted initiative that includes increasing overall access to naloxone ([The White House 2021](#)).

Analysis of Current Treatment Options

Since the approval of injectable naloxone in 1971, several strengths, dosage forms, and presentations have been approved; however, all naloxone products are only available by prescription. [Table 3](#) lists approved single-ingredient naloxone drug products in the United States.

Table 3. Currently Approved Single-Ingredient Naloxone Products*

Proprietary Name	NDA	Approval Date	Dosage Form or Presentation	Dose Route
Narcan	016636	4/13/1971 [§]	Solution for injection	0.4–2 mg IV, IM, SC
Evzio	205787	4/3/2014	Autoinjector	0.4 mg IM, SC
Narcan nasal spray	208411	11/18/2015	Nasal spray	4 mg IN
Evzio	209862	10/19/2016	Autoinjector	2 mg IM, SC
Narcan nasal spray	208411/ S-001	1/24/2017 [§]	Nasal spray	2 mg IN
Kloxxado	212045	4/29/2021	Nasal spray	8 mg IN
Zimhi	212854	10/15/2021	Prefilled syringe	5 mg IM, SC
Naloxone hydrochloride autoinjector [†]	215457	2/28/2022	Autoinjector	10 mg IM, SC
Naloxone hydrochloride nasal spray	208969	3/7/2023	Nasal spray	4 mg IN

Source: Reviewer summary

*This table does not include approved generic naloxone products

[§] Product withdrawn[†] Product is indicated for use by military personnel and chemical incident responders as treatment or temporary prophylaxis against the effects of high-potency opioids used as a chemical weapon

Abbreviations: IM, intramuscular; IN, intranasal; IV, intravenous; NDA, new drug application; SC, subcutaneous

Nalmefene hydrochloride is also indicated for the complete or partial reversal of opioid drug effects and management of known or suspected opioid overdose. It was approved in 1995 as an injection product to be given IV, IM, or SC. Like naloxone, it also carries cardiovascular risks and there is a risk of precipitated withdrawal. Unlike naloxone, however, its duration of action is longer than naloxone, and its safety and effectiveness have not been established in pediatric patients.

Important Regulatory History Related to This Application

This application was granted priority review status reflecting the importance of this product from a public health perspective. In addition, as the product represents a potential first-in-class product in a new therapeutic category for nonprescription drugs, a joint meeting of the Nonprescription Drugs Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee was held on February 15, 2023.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Efficacy of NNS Is Well Established as a Prescription Product for the Treatment of Opioid Overdose for All Ages, Including Neonates

3.1.1.2. Drug Facts Label and Pictograms Tested Well for Comprehension by Consumers

3.1.1.3. Availability of Nonprescription NNS Has the Potential to Address Barriers and Increase Naloxone Access to Consumers

3.1.2. Key Safety Review Issues

3.1.2.1. Naloxone-Induced Precipitated Withdrawal

3.1.2.2. Limited Efficacy

3.1.2.3. Device Use Errors and Additional Medication Errors

3.1.2.4. Limitations of Human Factors Validation Study Methodology

3.1.2.4.1. Pediatric Users Less Than 15 Years of Age Were Not Included in the HFVS

3.1.2.4.2. Two User Groups Did Not Include at Least 30% Limited Literacy Participants

3.1.2.4.3. Participants Were Allowed an Unlimited Familiarization Period

3.1.2.4.4. Moderators Employed Use of Leading Language and the “Think Aloud” Method

3.1.2.4.5. Mock Carton Labeling Tested in the HFVS Differs From the Intend-to-Market Carton Labeling

3.1.2.5. Qualitative Human Factors Validation Study Findings

3.1.2.5.1. Directions of the DFL Spanned Across the Back and Side Panels and Contributed to Use Errors, Close Calls, and Use Difficulties

3.1.2.5.2. Proposed User Interface Lacks Adequate Depiction of Correct Hand and Finger Positioning

3.1.2.5.3. Proposed DFL Directions on Nozzle Insertion Contributed to a Use Error

3.1.2.5.4. Proposed Labeling Does Not Adequately Communicate the Number of Doses Per Nasal Spray Device

3.2. Approach to the Clinical Review

The efficacy of NNS was established with its 2015 approval. The Applicant established a scientific bridge to NDA 016636 (naloxone hydrochloride for injection) utilizing the results of its pivotal relative bioavailability study. The bioavailability data demonstrated that NNS resulted in higher naloxone exposure concentrations than the reference naloxone hydrochloride 0.4 mg IM injection product at all time points, including the critical early timepoints of 2.5, 5, and 10 minutes postdose. The data supporting general efficacy as an opioid reversal agent are not in question for this sNDA, and new efficacy data were not required.

The safety of prescription NNS was supported by the results of the pivotal relative bioavailability study. The Applicant demonstrated that naloxone levels achieved with NNS were approximately five times that of 0.4 mg IM naloxone. This exposure was considered likely to fall well within the doses recommended in the approved Narcan injection labeling, which recommends up to a 2-mg initial dose and repeated doses every 2 to 3 minutes as needed. The label indicates that if no response is observed after 10 mg of Narcan have been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned.

To support the nonprescription application, the Applicant has conducted a review of domestic and foreign postmarketing safety data as well as the published literature related to intranasal naloxone (INN) between 2016 to 2021. Special attention was given to potential safety issues that may arise during nonprescription use. FDA has also conducted an independent review of the FDA Adverse Event Reporting System (FAERS) and the published literature for AEs related to INN occurring in

the community setting. Special attention was given to safety topics of naloxone-induced precipitated withdrawal, limited efficacy, and use errors (including device use errors as well as errors related to use of naloxone for the wrong indication and wrong storage conditions).

To support the nonprescription use of NNS, the Applicant has developed new packaging and labeling for its proposed nonprescription product. NNS's proposed DFL utilizes FDA's model naloxone DFL, which was tested and validated in a pivotal label comprehension study (LCS) and includes additional product-specific instructions. These modifications to the DFL along with other elements of the product's user interface (i.e., packaging, and additional labeling) were evaluated in a simulated use human factors validation study (HFVS) to demonstrate usability among groups of potential nonprescription users.

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☒	Other: (please specify)	Human Factors Validation Study discussed in Sections 7.7.4 and 7.7.5
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	Section 6.3.3 discusses barriers to naloxone access referenced by publications
☐	Patient-focused drug development meeting summary report	
☒	Other stakeholder meeting summary report	Section 12.1 highlights some public meetings that occurred that addressed barriers to access with stakeholders
☐	Observational survey studies	
☒	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

No new nonclinical data were presented in this sNDA for the assessment of effectiveness. This switch application is reliant on the original prescription application. Refer to the nonclinical

review of the prescription NDA 208411 by Drs. Newton Woo and Richard Mellon dated November 2, 2015 (DARRTS Reference ID: 3841831) and a nonclinical summary provided by Dr. Chibueze Ihunnah in Section [13](#).

5.2. Clinical Pharmacology/Pharmacokinetics

No new clinical pharmacology data were presented in this sNDA. This switch application is reliant on the original prescription application. Refer to the clinical pharmacology review of the prescription NDA 208411 by Drs. Suresh Narahariseti and Yun Xu dated October 22, 2015 (DARRTS Reference ID: 3841574, for full details. A high-level summary of the clinical pharmacology data is presented in Section [6.3.1](#).

6. Efficacy (Evaluation of Benefit)

The efficacy of NNS was established with its 2015 approval. The data supporting general efficacy as an opioid reversal agent are not in question and new efficacy data were not provided.

6.1. Assessment of Dose and Potential Effectiveness

Not applicable.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

Not applicable.

6.3. Key Efficacy Review Issues

6.3.1. Efficacy of NNS Is Well Established as a Prescription Product for the Treatment of Opioid Overdose for All Ages, Including Neonates

Background

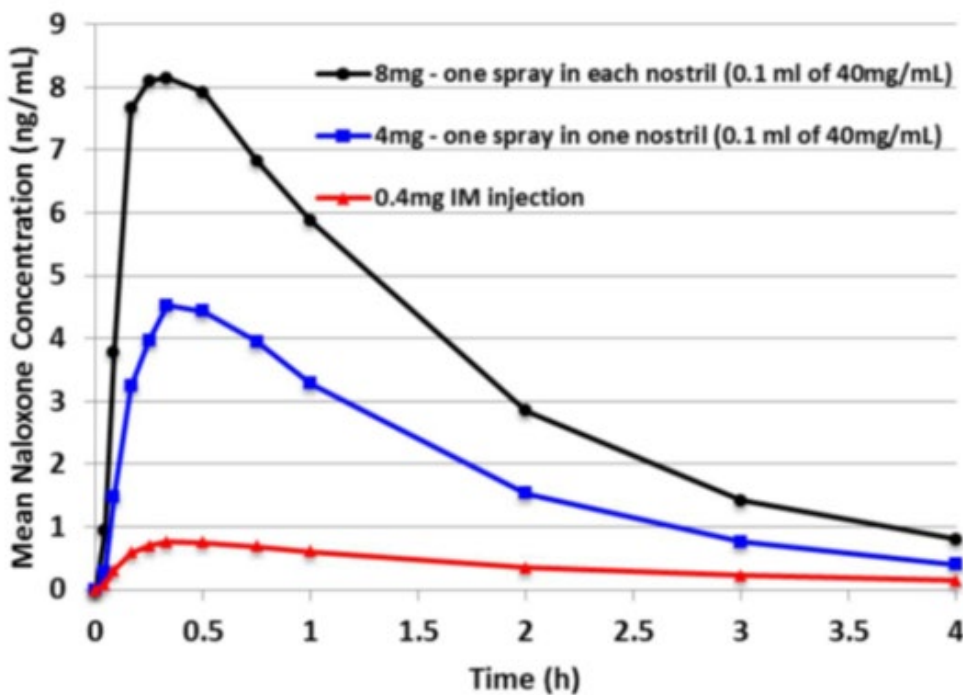
The original NDA 208411 for prescription NNS was submitted July 2015. Clinical trials were not performed to determine an effective dose range. The approach for establishing efficacy and approval of novel naloxone drug products was to demonstrate comparable or greater bioavailability to an approved naloxone product in healthy adult volunteers accompanied by data supporting the safety of the proposed naloxone dose. The novel naloxone drug product had to match or exceed the pharmacokinetic (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 016636) were used to establish efficacy for NNS. Since Narcan injectable solution had been discontinued from sale,¹ 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 (IN; n=30) and IM (n=29) naloxone administration to healthy subjects are shown in [Figure 1](#).

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 IM product at all time points, as listed in [Table 5](#).

Figure 1. 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. Ref ID:3837063
Abbreviations: IM, intramuscularly; IN, intranasally

¹ Discontinuation was not for reasons of safety or efficacy, as published in 74 FR 22751, May 14, 2009.

Table 5. 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	Test	Test		
	IM injection (0.4 mg)	One IN spray in one nostril (4mg)	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 original submission dated October 22, 2015, 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. However, due to the higher fixed dose of this product and the concern for 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 postoperative opioid reversal and for treatment of neonatal respiratory depression in newborns. For full details, please refer to Dr. Joshua Lloyd's summary review of the NDA dated November 18, 2015 (DARRTS Reference ID: 3848571).

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.

Conclusion

The Applicant seeks nonprescription marketing of NNS for the same indication, population, route, and dose as approved for the prescription-only product; therefore, no new clinical or pharmacokinetic studies were required or conducted to support the proposed nonprescription switch application. The general efficacy of this product as an opioid reversal agent in adults and

children, including neonates, was established with its 2015 approval and is not in question for this sNDA.

6.3.2. Drug Facts Label and Pictograms Tested Well for Comprehension by Consumers

Background

To encourage naloxone applicants to enter the nonprescription market and accelerate the development of nonprescription naloxone, FDA took the unprecedented approach to study, develop, test, and validate two versions of a model naloxone DFL. The model DFLs were developed by FDA clinicians and social scientists/communication experts with input from addiction treatment experts. One was developed for a nasal spray product, and one was developed for an autoinjector product. The Comprehension for OTC Naloxone (CONFER) pivotal LCS was then conducted to validate these DFLs. The study aimed to evaluate whether each model naloxone DFL could be read and understood in an emergency overdose situation by bystanders. If an applicant elects to use FDA's model naloxone DFL by adding only its product-specific instructions, then those labeling changes may be evaluated in a simulated HFVS. A summary of the pivotal LCS follows; however, full descriptions of the model naloxone DFL development process and the full LCS report are available on FDA's website ([Food and Drug Administration 2022](#)) and published in the *New England Journal of Medicine* ([Cohen et al. 2020](#)).

The Applicant's proposed NNS DFL utilized FDA's model naloxone DFL for a nasal spray ([Figure 2](#), column 1) as its foundation. The instructions for use (IFU) included the following:

- a. **Check** if you suspect an overdose
- b. **Give first dose** of Narcan over-the-counter (OTC) nasal spray; insert tip of the nozzle into either nostril and press the plunger
- c. **Call 911** immediately after giving first dose
- d. **Watch and give** continue to dose every 2-3 minutes until awake
- e. **Stay** until ambulance arrives; **Give** another dose if person becomes very sleepy again

Figure 2. FDA's Model Naloxone Drug Product DFLs for Use With Either a Nasal Spray or Autoinjector (Respectively)

Drug Facts	
Active ingredient (in each XX) Naloxone hydrochloride X mg	Purpose Emergency treatment of opioid overdose
Uses - To "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin - this medicine can save a life	
Directions  1 CHECK  2 GIVE  3 CALL  4 WATCH/GIVE  5 STAY Step 1: CHECK if you suspect an overdose: CHECK for a suspected overdose: the person will not wake up or is very sleepy or not breathing well - yell "Wake up!" - shake the person gently - If the person is not awake, go to Step 2 Step 2: GIVE 1st dose GIVE the 1st dose of this medicine - Insert in NOSE and press Step 3: CALL CALL 911 immediately after giving the 1st dose 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 Step 5: STAY STAY until ambulance arrives: even if the person wakes up GIVE another dose if the person becomes very sleepy again - You may need to give all the doses in the pack	
Warnings When using this product some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.	
Other information - store at room temperature - (advise insert tamper evident statement here)	
Inactive Ingredients	
Questions? (phone number, website)	

Drug Facts	
Active ingredient (in each XX) Naloxone hydrochloride X mg	Purpose Emergency treatment of opioid overdose
Uses - To "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin - This medicine can save a life	
Directions  1 CHECK  2 GIVE  3 CALL  4 WATCH/GIVE  5 STAY Step 1: CHECK CHECK for a suspected overdose: the person will not wake up or is very sleepy or not breathing well - yell "Wake up!" - shake the person gently - If the person is not awake, go to Step 2 Step 2: GIVE 1st dose GIVE the 1st dose of this medicine - Place the injector on the LEG above the knee and press down Step 3: CALL CALL 911 immediately after giving the 1st dose 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 Step 5: STAY STAY until ambulance arrives: even if the person wakes up GIVE another dose if the person becomes very sleepy again - You may need to give all the doses in the pack	
Warnings When using this product some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.	
Other information - store at room temperature - (advise insert tamper evident statement here)	
Inactive Ingredients	
Questions? (phone number, website)	

Source: Cohen et al., 2020, FDA Initiative for Drug Facts Label for Over-the-Counter Naloxone. New England Journal of Medicine, 382(22): 2129-2136.

Abbreviations: DFL, Drug Facts Label

Assessment

The study consisted of three tasks completed sequentially. In Task 1 of this study, FDA clinicians and social scientist/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 LL 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 2](#).

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 stepwise 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.

As shown in [Table 6](#), the study population included 473 normal literacy participants (66.6%) and 237 LL participants (33.4%). User segments included 430 adults who had either recently used opioids (Group 1) or family and friends of those who use opioids (Group 2). Another 280 “all comer” subjects were enrolled including adolescents ages 15 and above and adults. Males and females were represented equally (51% and 49%, respectively). The mean age was 37.6 years. There was racial diversity including 65.4% whites, 31.1% blacks, and 3.5% other. Additionally, 10% identified as Hispanic and 84% had a minimum of a high school diploma.

Table 6. 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%)

Variable	Overall n (%)	Normal Literacy n (%)	Limited Literacy n (%)
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
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%)

Variable	Overall n (%)	Normal Literacy n (%)	Limited Literacy n (%)
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

[Table 7](#) shows the primary and secondary endpoints for the pivotal LCS with a priori, targeted lower-bound thresholds displayed for the primary endpoints. Secondary endpoints do not have associated thresholds.

Table 7. Pivotal Label Comprehension Study Primary and Secondary Endpoints

Endpoints	Threshold (%)
Primary	
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 ²	
Note that some people may have symptoms when they wake up, such as shaking, sweating, having nausea, or feeling angry	NA
Note that it is safe to keep giving doses	NA
Give another dose if the person becomes very sleepy again	NA
Make sure that the "call 911" step is completed in the appropriate order relative to the other steps	NA
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	NA

Source: FDA reviewer's table.

¹ The target threshold for these end points 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 end points.

Abbreviations: NA, 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%.

[Table 8](#) shows the results for the LCS primary and endpoints, including point estimates (PEs) for the observed comprehension rates (percentage), and the upper and lower bounds of the 2-sided exact 95% confidence interval associated with the PE, where applicable.

Table 8. Results for the Label Comprehension Study Primary Endpoints

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: Backgrounder for Advisory Committee for NDA 208411 – S006 by FDA reviewer, B. Cohen
Abbreviations: LB, lower bound; N, number of subjects; UB, upper bound

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 of this endpoint 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.

In addition, results for the five secondary endpoints ([Table 9](#)) indicated that the associated DFL messages were well understood by most participants with PEs exceeding 80% for nearly all secondary end points, with the exception of the composite score 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. Results for the Label Comprehension Study Secondary Endpoints

Secondary Endpoints	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’s table.

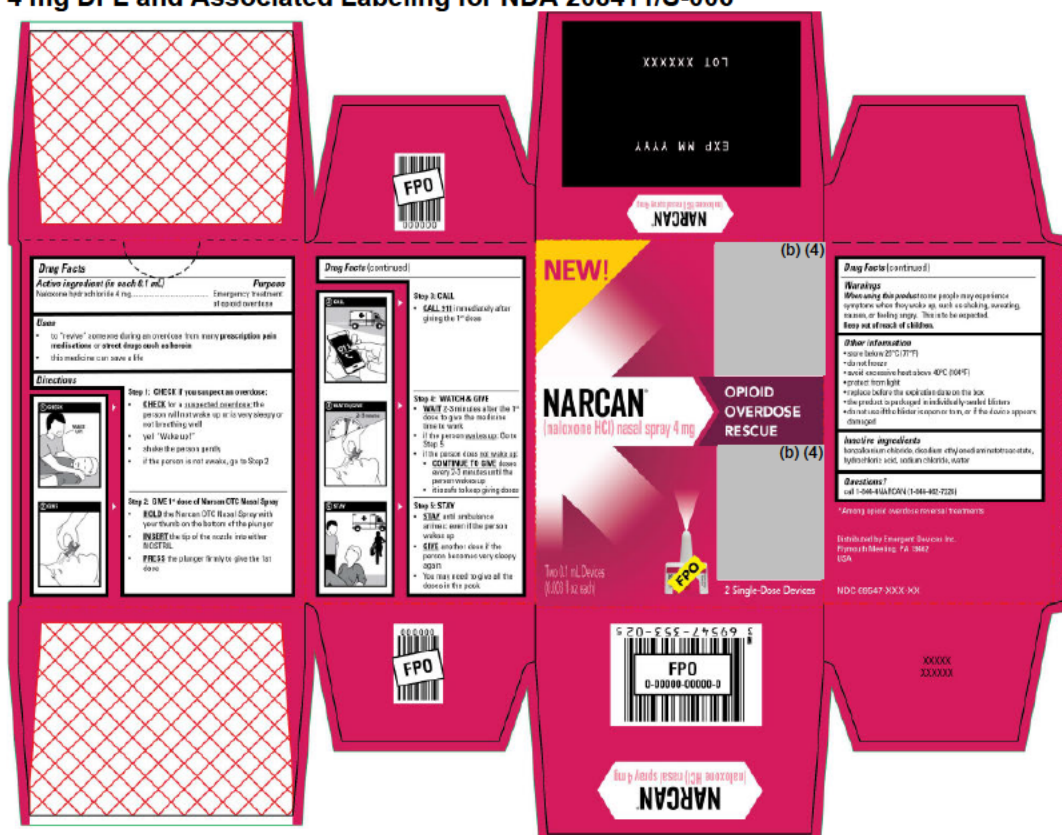
Abbreviations: NA, not applicable

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.

Conclusion

FDA’s model DFLs and their associated pictograms generally tested well for comprehension across groups in a pivotal LCS. There are some important distinctions between the FDA model naloxone DFL and the Applicant’s proposed DFL shown below (see [Figure 3](#)). A comparison of [Figure 2](#) (column 1) and [Figure 3](#) shows that there are some subtle differences between FDA’s model DFL and the Applicant’s proposed DFL, including (but not limited to) splitting the DFL across the back and side panels of the carton, and adding supplemental product-specific directions (Step 2). In this instance, the potential impact and implications of any differences between the Applicant’s proposed DFL and FDA’s model DFL are more appropriately handled in a well-designed HFVS. For more information on the Applicant’s HFVS, refer to the review by the Division of Medication Error Prevention and Analysis dated March 9, 2023 (DARRTS Reference ID: 5139093).

Figure 3. Applicant's Proposed Nonprescription Narcan (Naloxone Hydrochloride) Nasal Spray, 4 mg DFL and Associated Labeling for NDA 208411/S-006

Source: NDA 208411/S-006 submitted September 29, 2022

6.3.3. Availability of Nonprescription NNS Has the Potential to Address Barriers and Increase Naloxone Access to Consumers

Background

Reported barriers to accessing naloxone include lack of uniform pharmacy participation in naloxone distribution via naloxone access laws ([Correal 2018](#); [Meyerson et al. 2018](#)), stigmatization felt by consumers who try to access naloxone due to the need for interaction with a pharmacist to obtain prescription naloxone ([Evoy et al. 2021](#)), and inaccessibility of bulk purchasing of naloxone by harm reduction groups ([Lloyd 2018](#)).

Assessment

Pharmacies participate in naloxone distribution by stocking naloxone products and by actively dispensing the products. Whether a pharmacy stocks or dispenses naloxone currently depends on a number of factors, including consumer demand for naloxone in a given locality serviced by the pharmacy ([Lozo et al. 2019](#)) and pharmacists' familiarity with naloxone access laws as well as their perspectives on and comfort level with dispensing naloxone and willingness to do so

([Thakur et al. 2020](#)). Whether and to what extent a nonprescription version of naloxone will affect pharmacy stocking is unknown, although it is acknowledged that nonprescription switches typically do increase the availability of a product.

The approval of a nonprescription naloxone product can also help alleviate pharmacists' confusion related to naloxone access laws and remove any confusion about the legality of dispensing such a product. It will help pharmacists dispense naloxone in bulk to harm reduction groups who account for a large amount of distribution of naloxone to the public as well as to individuals.

Additionally, it is noted that if a naloxone product is switched to nonprescription status, it can be sold in retail settings besides pharmacies. Such settings may include gas stations, convenience stores, online retail, and vending machines set in communities where there may be high demand for naloxone. Availability of naloxone in these retail settings may further improve its penetration into communities that are inadequately served by pharmacies.

The stigma that consumers experience when requesting naloxone at the pharmacy is often cited as another major barrier of wider naloxone access because the current naloxone access paradigm requires a consumer to interact with a healthcare provider at the point of purchase. The possibility for increased anonymity with nonprescription purchases or the possibility of online pharmacy purchases makes it seem more likely that a nonprescription product will potentially address some aspects of stigmatization. Despite the lack of empirical data, it appears to be a reasonable assumption that the availability of a nonprescription naloxone product can potentially lower barriers of stigmatization.

Similarly, the effect of the proposed nonprescription product on access barriers faced by harm reduction groups may be addressed. An often cited hurdle faced by harm reduction groups is that despite currently available naloxone access laws, the official status of naloxone as a prescription drug blocks their ability to purchase naloxone products in bulk without significant administrative and legal challenges ([Pattani 2021](#)). The availability of nonprescription naloxone products may alleviate legal barriers faced by harm reduction groups, but the extent to which naloxone accessibility is addressed in this context will depend on the portion of the market currently accounted for by these bulk orders and this Applicant and others' ability to manufacture sufficient quantities of product at a reasonable cost. Nonetheless, it is noted that for these harm reduction groups, any improvement in accessibility is likely to be desirable.

It is acknowledged that economic factors such as manufacture price, insurance coverage, and consumer demand will likely have a large effect on naloxone accessibility. Murphy et al. aimed to predict the change in pharmacy sales following a prescription-to-nonprescription switch of naloxone ([Murphy et al. 2019](#)). Using mathematical modeling, the authors estimated that naloxone pharmacy purchases could increase by 15-179% even when adjusting for a range of potential variables including manufacturer price, out-of-pocket price increases that typically follow nonprescription conversions, and consumer demand.

Conclusion

The public health benefits of FDA-approved prescription naloxone products in preventing overdose deaths in the community may be extended with increased access to naloxone. We believe that a nonprescription naloxone option may provide a means to address some of the reported barriers to access naloxone and further improve overall naloxone availability.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No new nonclinical data were presented in this sNDA. This switch application is reliant on the original prescription application NDA 208411 that was reviewed by Drs. Newton Woo and Richard Mellon on November 2, 2015 (DARRTS Reference ID: 3841831). Additionally, a nonclinical summary of this information was written by Dr. Chibueze Ihunnah and included in Section [13](#) of this review.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Naloxone is generally administered in the setting of opioid use and many of the AEs described in approved Narcan labeling may be attributable to the reversal of the effects of the opioid. Narcan labeling describes the potential for precipitation of opioid withdrawal in opioid-tolerant patients characterized by 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 certain clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, exposure to naloxone may result in the abrupt precipitation of opioid withdrawal symptoms, including convulsions, excessive crying, and hyperactive reflexes.

Narcan labeling also notes that in the postoperative setting there have been postmarketing reports of hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest after using naloxone hydrochloride. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs, which may have similar adverse cardiovascular effects. Excessive doses of naloxone hydrochloride in postoperative patients have resulted in significant reversal of analgesia and have caused agitation.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

No labeling changes to the originally approved NNS prescribing information have been made due to safety concerns identified through its postmarketing experience.

For a discussion of postmarket safety for naloxone based on analyses of postmarketing safety databases, see Section [7.6](#).

7.4. FDA Approach to the Safety Review

The safety of NNS as a prescription product has been established in the United States since its approval in 2015 and supported by its seven years of domestic postmarketing experience. In addition, NNS has been marketed in Canada as a prescription product since 2016. The Applicant also notes that NNS has received marketing authorization in an additional seven countries (United Kingdom, Sweden, Ireland, France, Estonia, Germany, and Italy— all in 2018), though the product has not been launched in these countries.

The main consideration for this safety review is whether the drug can be used safely in a nonprescription environment in the United States without a learned intermediary.

To explore the safety concerns of NNS in the nonprescription space, the Applicant has conducted a review of domestic and foreign postmarketing safety data over a five-year period with special attention to potential safety issues that may arise during nonprescription use. The Applicant has also conducted a review of naloxone safety in the published literature. The primary value of these evaluations is to identify unexpected or serious events not previously recognized for naloxone products in general and, to the extent possible, to identify AEs and their relative frequencies specific to the proposed product. This evaluation utilized several postmarket safety databases including:

- The Applicant's own pharmacovigilance database (ARGUS)
- FAERS
- World Health Organization's (WHO) Vigibase

The Applicant has also given special attention to several relevant safety topics of interest including use in vulnerable populations (pediatrics, pregnancy, the elderly), use errors, product ineffectiveness, drug hypersensitivity, and acute opioid withdrawal syndrome. For the purposes of this integrated review, the assessment of the Applicant's analysis of ARGUS is included in Section [7.6](#). The assessments of the Applicant's analyses of FAERS and WHO Vigibase is included in Section [17](#).

The Office of Surveillance and Epidemiology (OSE) was consulted to evaluate AEs occurring in association with naloxone products (all routes of administration and a subset analysis of INN cases occurring in the community setting). This independent review of FAERS and the published literature gives special attention to safety topics of naloxone-induced precipitated withdrawal, limited efficacy, and use errors (including device use errors as well as errors related to use for the wrong indication and wrong storage). High level summaries of these safety topics are provided in Sections [7.7.1](#), [7.7.2](#), and [7.7.3](#), respectively; for a full review, please refer to the OSE Consult Review dated February 27, 2023 (DARRTS Reference ID: 5131876).

To support the nonprescription use of NNS, the Applicant has developed new packaging and labeling for its proposed nonprescription product. The product's user interface (i.e., packaging, and additional labeling) was evaluated in a simulated-use HFVS to assess whether it is adequately designed to support the intended users of the proposed nonprescription product. High level summaries of key HFVS limitations and findings are provided in Sections [7.7.4](#) and [7.7.5](#), respectively; for a full review of the HFVS qualitative data, please refer to the Division of Medication Error Prevention and Analysis Review dated March 9, 2023 (DARRTS Reference ID: 5139093).

7.5. Adequacy of the Clinical Safety Database

Data for clinical safety that were generated in the pivotal comparative bioavailability study were submitted and reviewed in the original prescription NDA and were considered adequate. Those data were not reviewed again here.

For the purpose of this nonprescription application, the safety database included the Applicant's evaluation of postmarketing safety data and published literature. These were conducted according to expectations of a nonprescription application and considered adequate to support the review.

7.6. Safety Results

As noted above, the Applicant conducted a review of domestic and foreign postmarketing safety data over a five-year period across three pharmacovigilance data sources: the company's pharmacovigilance database ARGUS, FAERS, and WHO Vigibase. Of these three data sources, ARGUS provides the most pertinent observations of AEs occurring with INN as most of the cases collected within this database reported NNS as the suspect product. The Applicant's analysis of FAERS data included information from all routes of naloxone administration, which allowed for comparison of AEs generated from cases all involving INN versus non-nasal routes. The Applicant's analysis of WHO Vigibase was predominantly limited to cases involving INN products and served as a confirmatory analysis of the ARGUS and FAERS findings. For the purposes of this integrated review, the assessment of the Applicant's analysis of ARGUS will be included in this section. The assessments of the Applicant's analyses of FAERS and WHO Vigibase is included in Sections [17.1](#) and [17.2](#).

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. Therefore, an AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with use of a drug product. Case reports categorized as having 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.

All postmarketing databases are susceptible to inherent limitations including, but not limited to under-reporting, lack of reporting standards, incomplete reporting, duplication, reporter bias, and the presence of potential confounding factors within a case that preclude a causal assessment. Of the three databases, the Applicant was only able to access case narratives within ARGUS to allow for further assessment and medical confirmation of the AEs reported. Additionally, there is no way to know the true denominator of patient exposure or true number of cases for any AE. These issues limit our ability to draw definitive conclusions based on the postmarketing experience; nevertheless, analyses of this information for INN can provide some useful insights as to the safety performance of the proposed product.

7.6.1. Postmarket Safety Evaluation From the Applicant's Pharmacovigilance Database

The Applicant was requested to collect postmarketing safety data relating to naloxone products in its company pharmacovigilance database, ARGUS. This analysis was submitted November 2, 2022, in the Applicant's response to FDA's initial Information Request and amended November 22, 2022. The evaluation covered the period from January 1, 2016, through June 30, 2021. The medical dictionary used for this search was Medical Dictionary for Regulatory Activities (MedDRA) version 25.0.

As ARGUS is the Applicant's own pharmacovigilance database, it is the most robust source of postmarketing safety information available for INN, but it could include products other than NNS, such as other approved intranasal naloxone products or injectable naloxone administered using a nasal atomizer. The Applicant notes that this safety database contains cases presumed to be related to the use of its product, NNS, and not naloxone 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." Case narratives were also available in the ARGUS database, which allowed for more detailed evaluation of cases.

Estimated Patient Exposure

To provide a rough estimate for postmarketing patient exposure to Narcan, the Applicant provided its cumulative product distribution by year. From launch of NNS in February 2016 through June 2021, the Applicant reported a cumulative distribution of (b) (4) unit cartons in the United States and (b) (4) unit cartons distributed elsewhere (b) (4). Each carton contains two, 4 mg nasal spray devices, which means that approximately (b) (4) doses have been distributed domestically by the Applicant over 5.5 years. The Applicant was unable to provide estimates on the distribution of other naloxone products domestically or worldwide.

General Findings

During the reporting period, a total of 397 unique case reports were identified that reported over 900 AEs. Most cases were reported in individuals in the 18- to 65-year-old demographic (55%) and slightly more cases were reported in males (51%) than in females (41%) when age and gender were known. Notably, age was unknown for 37.8% of cases.

Serious Outcomes

The Applicant noted that serious outcomes occurred in 93 (23.4%) cases, including 26 cases that resulted in a fatal outcome. Notably, most cases with serious outcomes occurred in adults 18 to 65 years of age, matching the demographic who most frequently use opioids. No serious outcomes occurred in children less than 2 years.

The Applicant's information indicated that out of 93 cases with serious outcomes, a total of 332 AEs were identified. Some of the most frequently appearing preferred terms (PT) among cases

reporting serious outcomes included death (14 cases),² drug withdrawal syndrome (12 cases), seizure (12 cases), loss of consciousness (7 cases), toxicity to various agents (6 cases), and vomiting (6 cases). [Table 10](#) shows the most frequently reported PTs appearing >1% among serious cases.

Table 10. Preferred Terms Appearing >1% Among Cases Reporting Serious Outcomes

Preferred Term	<2 yrs. n=0	2–<18 yrs. n=23	18–<65 yrs. n=206	≥65 yrs. 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: Adapted from Module 5.3.5.3 Emergent (ARGUS) Safety Database Analysis, submitted November 22, 2022, Appendix I, page 16

Cases Reporting Death as an Outcome

There was a total of 26 fatal cases (26/397, 6.5%) for which narrative summaries were provided. Careful evaluation of these narratives showed that nine cases reported toxicity to various agents besides opioids as a cause of death. Two cases reported that the victim had been down too long before being administered naloxone. Most fatal cases (15/26, 57.7%) contained too little information to show an association between naloxone and the fatal outcome, including temporal information to establish product ineffectiveness. One case described a clinical scenario where INN had been used inappropriately by police responders to a 911 call. Naloxone was given for presumed opioid overdose when the patient was experiencing an asthma exacerbation. It is unclear why the patient did not receive treatment for asthma. Reportedly, the naloxone treatment was followed by a severe worsening of asthma symptoms and subsequent death.

A search of the published literature did not demonstrate any associations between naloxone and asthma exacerbation. Snorting or smoking heroin and other opioids is known to induce pulmonary bronchoconstriction ([Tataris et al. 2013](#)); however, no studies appear to have demonstrated a positive or negative effect of naloxone on bronchospasm.

The above findings are commonly associated with cases of opioid overdose. Victims frequently misuse or abuse several drugs, which may or may not be affected by naloxone. Timing of

² The number of cases reporting “death” as a preferred term (n=14) is not the same as overall cases reporting a fatal outcome (n= 26) because other terms can be used to indicate death (e.g., brain death) or the case can be marked as having a fatal outcome with no preferred term reported.

naloxone administration relative to the opioid overdose is also a critical factor. Fatality is common in these scenarios.

Special Populations

Pregnancy

The Applicant conducted an assessment to evaluate use of naloxone in pregnancy and identified four such cases. Among the four cases, there was one serious outcome of premature delivery in a patient who was using multiple drug products including Abilify, buprenorphine, diazepam, Vyvanse, and nicotine. Another case resulted in a nosebleed and general aggression after use of Narcan and two other cases did not yield useful information (i.e., reported exposure but no specific adverse reaction). None of the cases resulted in fatal outcomes.

There does not appear to be a strong association between naloxone use in pregnancy and any specific types of adverse outcomes reported. The one case reporting premature delivery appeared to be confounded due to use of multiple drug products and nicotine during pregnancy. Most cases did not yield useful or significant information.

Pediatrics

The Applicant conducted an assessment among the pediatric population. A total of eight cases were reported in patients less than 18 years of age and summaries for these eight cases were provided.

Five cases occurred in older children (>12 years) with four of the five reporting serious outcomes. Three serious cases reported use of naloxone in an unapproved indication where the overdose occurred with a nonopioid agent. AEs reported in association with these three cases, including two deaths, appeared to be more likely associated with the underlying drug of overdose rather than naloxone. In the remaining serious case, a 17-year-old received naloxone after an opioid overdose and experienced seizure and several mini strokes. In the last case occurring in an older child, a 17-year-old received naloxone after overdose with heroin and oxycodone and experienced vomiting and anger.

Three other cases occurred in young children. One case described use of Narcan in an infant (exact age not reported) who had possibly gotten access to heroin; the infant was taken to the hospital where a drug screen was found negative. A second case occurred in a toddler (exact age not reported) who was found unresponsive and was revived after administration of Narcan though a blood/urine analysis later revealed phencyclidine but no opioids. A third case described a child (exact age not reported) who reportedly had taken fentanyl and Narcan; however, the child was described as not being overdosed and Narcan was described as being incorrectly administered (PT unintentional use for unapproved indication). No additional AEs were noted in any of these three cases.

There does not appear to be a strong association between naloxone use among children and any specific types of adverse outcomes reported. In a majority of the cases, AEs (including the two reported fatalities) appeared to be related to the underlying nonopioid drug of overdose. In six cases, naloxone was used where no opioid overdose had occurred; however, no pattern of adverse outcome was noted. Of the two remaining cases, patients experienced known AEs associated with naloxone. The vomiting and anger reactions noted in one patient may be

associated with naloxone; however, these are not considered life-threatening. The seizure and ministrokes experienced by the other patient are concerning. However, considering the underlying condition is opioid overdose, the outcome of which is near certain death without prompt treatment such as naloxone or emergency intubation to restore respiration, the overall benefit risk assessment for naloxone use in that scenario is still favorable.

Geriatrics

The Applicant conducted an assessment among the geriatric population. A total of 21 cases were reported in patients greater than or equal to 65 years of age. Five cases reported serious outcomes with 56 AEs; none were reported as fatal. For this age group, the system organ classes (SOC) most frequently noted were Nervous System Disorders, Investigations, and Infections. No single preferred term within Nervous System Disorders appeared predominant; unresponsive to stimuli appeared the most at two times and is likely related to the underlying intoxication event rather than naloxone use. Under the Investigations and Infections SOC, similarly, no single PT appeared predominant; however, blood culture positive appeared three times, while oral candidiasis, pseudomonas, and strep infection each appeared twice. These also do not appear to be related to naloxone use. There does not appear to be any AE that occurs disproportionately in the older population.

Safety Topics of Interest

Use Error

The Applicant evaluated its company pharmacovigilance database for cases involving naloxone that resulted in a serious outcome related to use error. The Applicant identified 11 unique cases (11/397; 2.8%) that reported a PT within the MedDRA High Level Group Term “medication errors and other product use errors and issues”, including three cases that had a fatal outcome.

Case narratives were provided for review.

- Five cases reported use in an unapproved indication, including four cases where consumers administered Narcan because they thought it was a sinus or nasal spray and subsequently experienced withdrawal symptoms considered to be serious. One case described a patient who mistakenly took Narcan for a nasal treatment and later experienced a fatal cardiac arrest. In another case, Narcan was administered for the wrong indication as the patient was given Narcan for her asthma exacerbation and died.
- In one case, the error was related to the wrong route of administration as Narcan was reportedly administered in the arm.
- Five additional cases were reviewed, including one case that had a fatal outcome; however, details from these cases were too limited to confirm the use error.

Overall, use errors do not appear to be a major safety signal; though, there did appear to be some confusion with other nasal products. In at least one case, it was reported that the patient was a chronic user of prescribed opioids and had received Narcan through the mail after discussion with his physician before mistakenly using it as a sinus treatment. It is possible that consumers who intentionally seek to purchase a nonprescription naloxone product may be less prone to this type of error. To further mitigate the risk of this use error, the nonprescription labeling for NNS

will also emphasize its indication clearly in several locations on the packaging via its Statement of Identity and its Uses.

Product Ineffective

The Applicant evaluated its company pharmacovigilance database for cases involving naloxone that resulted in a serious outcome related to product ineffectiveness. The Applicant identified 10 cases (10/397; 2.5%) that reported a PT of “drug ineffective”, including two cases with a fatal outcome.

Case narratives were provided for review.

- Five cases reported multiple drugs being used in the overdose, including three cases where benzodiazepines and alcohol were concomitantly used and one case where the patient was suspected of having an opioid overdose, but instead took desvenlafaxine and amitriptyline in a suicide attempt. Naloxone is not expected to reverse the sedative effects of nonopioid substances. One case described the patient as purple and “already dead” by witnesses before Narcan administration and reported a fatal outcome. Naloxone is not expected to reverse opioid overdose in scenarios where the time to administration from the onset of overdose symptoms is prolonged.
- The remaining case described a patient who was found down and upon a friend administering Narcan, it was reported that “nothing came out”; however, the patient was administered cardiopulmonary resuscitation and subsequently recovered.
- In four additional cases, there was inadequate temporal detail to confirm that the product was ineffective, including the other case with a fatal outcome.

Overall, these product ineffective cases do not appear to indicate that the product is ineffective if used according to the label. See Section [9](#) for more discussion on device reliability.

Drug Allergy and Hypersensitivity

The Applicant evaluated its company pharmacovigilance database for cases involving naloxone that resulted in a serious outcome related to drug allergy. The Applicant identified three cases (3/397; 0.8%) that reported a PT within the MedDRA High Level Group Term “allergic conditions” and provided case narratives for review. None of the cases reported a fatal outcome.

Case narratives were provided for review.

- One case described a patient with known naloxone hypersensitivity who developed anaphylactic shock after being administered naloxone for a suspected overdose. The case outcome was listed as recovered.
- Two cases reported too limited details to confirm whether AEs were related to naloxone use or multiple other concomitant drugs.

Naloxone is contraindicated in patients known to be hypersensitive to it; nonetheless, it is reassuring that very few cases were reported overall, and the one confirmed case indicated recovery from both the allergic reaction as well as the opioid overdose. Overall, there does not appear to be a major safety signal for drug hypersensitivity. As opioid overdose is a life-threatening condition and hypersensitivity reactions to naloxone appear infrequently, the benefit-

risk consideration for using naloxone in the setting of potential hypersensitivity is still generally favorable.

Acute Opioid Withdrawal

The Applicant evaluated its company pharmacovigilance database for cases involving naloxone that resulted in a serious outcome related to opioid withdrawal syndrome. Opioid withdrawal syndrome occurs in the setting of abrupt discontinuation or reversal of drugs in individuals who have opioid dependence. For individuals who are opioid dependent, withdrawal can lead to a variety of symptoms, including body aches, pain, fever, diaphoresis, rhinorrhea, sneezing, piloerection, yawning, weakness, asthenia, rigors, tremor, seizure, restlessness, irritability, aggressive behavior, diarrhea, nausea, vomiting, abdominal cramps, increased blood pressure, and tachycardia. The degree of physical dependence, the dose and potency of the opioid that induced the overdose, and the dose administered of reversal agents like naloxone can all influence the severity of opioid withdrawal syndrome. Though acute opioid withdrawal can be very unpleasant to experience, with few exceptions, it is generally not considered life-threatening. The known exceptions may include situations involving cardiac arrest, cardiac arrhythmias, pulmonary edema, and seizures.

The Applicant was requested to create a custom query to extract cases of potential acute withdrawal symptoms resulting in serious outcomes related to life-threatening manifestations of withdrawal. The Applicant's query included the standardized MedDRA query "drug withdrawal" as well as a variety of signs and symptoms often associated with opioid withdrawal. Any case that contained a PT from the case definition and resulted in a serious outcome was reviewed to determine whether the case described a potential opioid withdrawal scenario. The Applicant identified 27 cases (27/397; 6.8%) of acute opioid withdrawal resulting in serious outcomes, including two with fatal outcomes. Note that the Applicant's investigation of this topic differed from FDA's independent review (see Section [7.7.1](#) for a high-level summary and the OSE Consult Review for full details) as the Applicant only looked at the case narratives for the 27 cases that included a serious outcome. The Applicant also did not attempt to objectively quantify the severity of opiate withdrawal symptoms.

Case narratives were provided for review.

- Eleven cases described clinical scenarios in which patients experienced life-threatening manifestations of acute opioid withdrawal. One case resulted in a fatal outcome due to respiratory failure. The most frequently reported life-threatening manifestations were seizures in eight cases. In the two remaining cases, one described ventricular tachycardia with a heart rate over 200 beats per minute, and one described syncope.
- Seven cases described scenarios in which the withdrawal symptoms were not considered life-threatening, or the symptoms described were considered unrelated to withdrawal syndrome, including a case with fatal outcome.
- The remaining nine cases lacked adequate detail to determine if symptoms were due to withdrawal (e.g., due to concomitant medical conditions), or it was unclear whether the withdrawal symptoms were life-threatening (e.g., no additional detail provided of the specific AEs aside from "drug withdrawal").

Opioid withdrawal is a known potential AE related to naloxone use that is typically not life-threatening. Overall, the analysis conducted by the Applicant within ARGUS is reassuring that the number of opioid withdrawal cases leading to life-threatening AEs appears to be small and those leading to fatal outcomes is even smaller.

Rebound Opioid Toxicity

Rebound opioid toxicity is the re-emergence of an opioid overdose manifestation such as respiratory depression, following the temporary reversal of opioid overdose with naloxone. Repeat doses of naloxone are sometimes required as the duration of action of many opioids exceeds that of naloxone; thus, re-emergence of opioid overdose symptoms is possible.

The Applicant attempted to evaluate cases of rebound opioid toxicity in its postmarketing safety database. However, it noted that because NNS is used in the community setting and there is an inability to medically confirm or follow up a majority of cases, any evaluation of the database precludes a meaningful assessment. Additionally, the Applicant notes that rebound opioid toxicity is not a searchable diagnosis and retrieved no cases of this condition. Therefore, no attempt was made to evaluate the reported cases for this issue. The Applicant concludes that the benefit of NNS outweighs the risk of rebound toxicity.

It is agreed that evaluation of the postmarketing database for rebound toxicity is unlikely to yield useful information. Because the symptoms of initial opioid overdose and rebound toxicity are the same, it would not be possible to isolate cases of rebound toxicity using specified search terms. Furthermore, rebound opioid toxicity is not an AE directly associated with naloxone use. When it occurs, it suggests that more naloxone is needed in the clinical scenario. Though there are no data indicating rebound opioid toxicity occurring in the ARGUS database, the concern for rebound opioid toxicity seems to be an argument in favor of even greater naloxone accessibility. The response to rebound opioid toxicity should be to administer additional doses of naloxone. Having a naloxone product available as a nonprescription product may increase the availability and accessibility to allow for repeated administration. Additionally, the NNS prescribing information indicates that the mean plasma half-life of a 4 mg NNS dose in healthy adults is approximately 2.08 hours. The nonprescription labeling for naloxone emphasizes the importance of “Call 911” as a key step in the instructions for use. If NNS is used according to the label, calling 911 should activate emergency medical services early and help mitigate issues that may arise from rebound opioid toxicity.

Reversal of Respiratory Depression in Cases of Nonopioid Use or Partial Opioid Agonist Use

Naloxone is not expected to be effective in reversal of respiratory depression due to nonopioid use and is expected to be less effective when used against partial opioid agonists or highly potent opioids. The Applicant attempted to evaluate this clinical scenario by searching for cases reporting respiratory depression. Nineteen cases were identified using this search method and case narratives were provided. However, most cases were irrelevant to this topic. None of the cases provided adequate detail to confirm that naloxone was ineffective or only partially effective due to use against a nonopioid or partial opioid agonist. This result is not surprising given the search method utilized. Respiratory depression is a symptom of opioid overdose as well as in scenarios where there is ineffective or partially effective reversal. It may not be possible to isolate cases of partial effectiveness or ineffectiveness due to other substances

because of database limitations of incomplete reporting. Furthermore, it appears that whether there are cases of ineffectiveness due to use of nonopioids or partial effectiveness due to use of partial opioid agonists may not influence our considerations of Narcan in the nonprescription space as an empiric trial of naloxone may be appropriate regardless.

7.6.2. Published Literature

The Applicant conducted a literature search using EMBASE covering the period January 1, 2016, to October 1, 2022. The objective of this search was to identify new safety information related to naloxone use in the community setting, including safety topics of special interest such as device and medication errors, clinical studies, educational programs, storage and handling, unexpected events and risks, special populations, and efficacy. The Applicant provided a detailed search strategy for identifying relevant information regarding naloxone safety.

Out of 316 articles initially identified, the Applicant provided 59 references for review, including 41 articles and 18 case reports.

Five articles that were published both before the approval 2015 of NNS and afterwards generally discussed the favorability of naloxone use by laypersons. The most recent article ([Pergolizzi et al. 2021](#)) noted that the increasing abuse of superpotent opioids may necessitate consideration about the efficacy of naloxone in these clinical scenarios. See the additional literature review conducted by FDA below for more information.

The Applicant identified thirty-six other articles as relevant to safety topics of special interest including opioid withdrawal, product use, education, access, and availability. Two articles were submitted on the topic of opioid withdrawal, but neither provided information relevant to this review. One article submitted on the topic of storage and stability of naloxone products appeared to support expiration dates up to 10 months longer for naloxone nasal spray products when they were stored properly. Nineteen articles were submitted on the topic of product use, education, access, and availability; however, almost all the articles (18) described the effects of naloxone education training, and none of the 19 articles were related to the AE profile of naloxone. Therefore, none of these articles were relevant to this review. Fourteen articles were submitted on the topic of community use naloxone products. Of these, five focused on general attitudes about naloxone use in a community setting, three focused on socioeconomic factors related to distributing naloxone in the community, and four described trials related to naloxone education/training and the general benefits thereof. These 12 articles were of little relevance to this safety review as they did not speak to safety issues or AEs related to naloxone use.

Two remaining articles described aspects related to the safety of naloxone and were generally considered favorable to INN:

- Alho et al. described a randomized controlled trial studying INN as a potential treatment in otherwise healthy gambling addicts ([Alho et al. 2022](#)). Study subjects were randomized to 4 mg naloxone nasal spray up to four times a day or placebo nasal spray as needed in response to a gambling urge. The authors reported an overall compliance rate of 70% but did not provide the average number of doses received by subjects in the treatment arm. Nevertheless, all AEs related to naloxone treatment were noted to be mild. Though the most common AEs were related to nasal congestion or irritation (28/62; 45.2%), nasal mucosal assessments and smell tests conducted showed no difference when compared with placebo.

- Alsharif et al. presented an abstract describing the frequency of AEs occurring in patients who received intranasal versus intravenous/intraosseous prehospital naloxone before being treated at their hospital ([Alsharif et al. 2021](#)). Of 778 cases meeting criteria, 670 patients received INN, while 108 received intravenous or intraosseous naloxone. Patients receiving IV/intraosseous naloxone were 14.6% more likely to suffer any AE compared with 7.8% who received nasal forms of naloxone. No difference was noted in the frequency of improvement in respiratory status by either naloxone route. The authors concluded that the findings supported preferential administration by the intranasal route.

The Applicant also compiled 18 case reports that identified serious AEs in the setting of naloxone use:

- Half of the articles (9) described clinical scenarios where the symptoms noted in the article were later determined to be secondary to another non-naloxone related etiology (e.g., the events noted were manifestations of the patients' nonopioid overdose or other medical conditions).
- Four other articles described AEs that are unclearly associated with naloxone:
 - Kline et al. wrote about the perspective of patients who use drugs that there is a necessity to treat opioid withdrawal symptoms after naloxone use, because those withdrawal symptoms have led some to overdose again ([Kline et al. 2020](#)).
 - Kahn et al. wrote about at least one patient who experienced worse emotional responses since being treated with naloxone, although the drug was acknowledged to have saved their life ([Kahn et al. 2022](#)).
 - Aguirre et al. described unusual memory impairment following naloxone exposure in the setting of polysubstance abuse ([Aguirre et al. 2021](#)).
 - Leung et al. described a case where a death occurred despite using naloxone in a clinical scenario where opioid overdose was suspected; however, there was no confirmation of the overdose substance in that case ([Leung et al. 2021](#)).
- Five articles described AEs where naloxone is more likely related:
 - Four articles described a total of 14 cases of pulmonary edema following naloxone use. Kummer et al. described a case study of 10 patients who developed naloxone associated pulmonary edema after recreational opioid use, including 4 patients who developed acute onset respiratory distress and severe hypoxemic respiratory failure ([Kummer et al. 2022](#)). It was noted that all 4 patients experienced rapid resolution of their conditions within 48 hours and were eventually discharged. It was also noted that the onset and severity of the respiratory failure was not dose dependent, which the author believes suggests that there may be other important risk factors.
 - The final article described a case of severe prolonged agitation after being dosed a total of 24 mg INN for a fentanyl overdose.

Overall, the Applicant's conclusion was that the literature did not identify any new safety information or any increase in severity or frequency of known safety risks of expected AEs.

Additional Literature

FDA conducted an additional search of the published literature to evaluate higher concentration INN products (such as Narcan) 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 through 2022 (the years since Narcan's launch), the search identified very few articles specifically addressing higher concentration INN products. Many articles covered naloxone use from all routes of administration and often discussed multiple naloxone administrations of various doses, formulations, and routes equivalently. Two articles specifically addressed higher concentration INN.

A 2018 article by Avetian et al. 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 ([Avetian et al. 2018](#)). Eight organizations reported a total of 261 attempted opioid overdose reversals using NNS between April to 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), 97.6% (248/254) required one or two doses, 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% (242/245) were reported as successful. Of the three deaths reported, NNS was reported administered too late in two individuals and details were not provided for the third case.

A more recent article by Abdelal et al. 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 ([Abdelal et al. 2022](#)). 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. 30% 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. 95% 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.

These 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.

7.7. Key Safety Review Issues

7.7.1. Naloxone-Induced Precipitated Withdrawal

Background

OSE was consulted to evaluate FAERS for AEs occurring in association with naloxone products (all routes of administration and a subset analysis of INN cases occurring in the community setting). Naloxone-induced precipitated withdrawal was previously identified in the prescribing information as a serious AE that occurred with some frequency. The condition has the potential to be life-threatening. Seizures, cardiovascular events, and pulmonary edema have all occurred

as a result of naloxone-induced opioid withdrawal. For this reason, the postmarketing safety data were evaluated for cases of naloxone-induced opioid withdrawal among those cases involving INN in the community setting. For a full review, please refer to the OSE Consult Review (DARRTS Reference ID: 5131876).

Assessment

In order to assess opiate withdrawal in the subset of INN cases selected, the Clinical Opiate Withdrawal Scale (COWS) was used to evaluate all 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. Although the COWS scoring tool is intended for use at the bedside to rate opiate withdrawal symptoms, we used it to identify and assess withdrawal symptoms in case reports because it provided an objective way to do so.

Based on our case definition of naloxone-induced precipitated withdrawal, a case met the definition if either a healthcare professional or a layperson reported opioid withdrawal after naloxone administration and case details, such as specific signs and symptoms associated with the COWS, supported that diagnosis. 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 been higher.

A total of 318 cases were identified that described INN use in the community setting. Among the 318 cases, a total of 180 cases (180/318, 56.6%) were identified reporting withdrawal or symptoms consistent with withdrawal. No deaths were reported and 35 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 and no cases exceeded a score of 12. 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 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” ([Emergent Devices Inc. 2020](#)).

Conclusion

Cases reported in FAERS reflect the known AE of naloxone-induced precipitated withdrawal, which is included in the prescription naloxone labeling under Warnings and Precautions and is reflected in the proposed DFL in consumer-friendly language. 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](#)).

The findings from the OSE review which was much more exhaustive than the Applicant's review of the cases that were deemed "serious" suggest that although symptoms of naloxone-induced precipitated withdrawal are reported with some frequency (56.6% of INN cases were identified with the condition), only a small subset reported serious outcomes (35/318; 11%) and no fatalities were reported. On balance, as naloxone treats opioid overdose and may save the life of the patient, the benefits of naloxone outweigh the risk of precipitated withdrawal.

7.7.2. Limited Efficacy

Background

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 superpotent opioids are involved, if time elapsed between when the overdose occurred and when naloxone is administered, and the administration technique. Naloxone needs to be administered as promptly as possible after overdose to prevent mortality and morbidity.

OSE assessed FAERS for cases of limited efficacy to determine if there were any trends or patterns as to the reason for decreased efficacy and if mitigating factors could be identified such as improved labeling of the proposed nonprescription product or improvements to the nasal spray device. Additionally, as the opioid crisis has shifted in recent years with increased use of higher potency opioids, such as fentanyl, this was an opportunity to review the postmarketing data collected during this interval to evaluate for any trends that might suggest whether NNS 4 mg provides an adequate dose of naloxone. For a full review, please refer to the OSE Consult Review (DARRTS Reference ID: 5131876).

Assessment

The 318 cases describing INN use in the community setting were evaluated for mentions of AEs 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. In one of the two fatal cases, polysubstance overdose was reported, including alprazolam and alcohol. The most common reasons reported for limited efficacy included being "too late" or an unknown amount of time had elapsed since the overdose occurred (6/24, 25%), various product issues such as "nothing came out" (5/24, 20.8%), no response to a first dose though there was a response to a second dose (5/24, 20.8%), and not having enough naloxone (2/24, 8.3%). Six cases (6/24, 25%) provided no reason at all.

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.

Conclusion

As noted above, many factors contribute to whether naloxone use will be effective. Delayed or unknown timing of naloxone administration after the overdose event was the most common factor appearing in at least 25% of limited efficacy cases. Cases reporting product issues such as “nothing came out” may have been related to use errors, but limited information precluded a meaningful assessment. It is noted that all devices are assessed for robustness at approval and manufacturers are expected to comply with cGMP regulations at all times. See Section 9 for a discussion about device reliability. Overall, there was a small number of cases identified with limited efficacy. Additionally, it is noted that the nonprescription labeling for NNS will instruct users to “Call 911” as a key step, which should activate emergency medical services in the event that a patient does not respond to naloxone for any reason.

7.7.3. Device Use Errors and Additional Medication Errors

Background

OSE assessed FAERS for cases of device use error and additional medication errors associated with prescription NNS and Kloxxado nasal spray to determine if there were any trends or patterns as to the reason for device use errors and if mitigating factors could be identified and addressed in the labeling or product/package design. For a full review, please refer to the OSE Consult Review (DARRTS Reference ID: 5131876).

Assessment

A separate FAERS search was conducted for device use errors and medication errors involving prescription NNS and Kloxxado nasal spray. The National Coordinating Council for Medication Error Reporting and Prevention Taxonomy of Medication Errors was used to describe the type of medication error and contributing factors ([National Coordinating Council for Medication Error Reporting and Prevention 2023](#)). The following exclusion criteria were applied: scenarios of naloxone hydrochloride nasal spray device malfunction, cases where insufficient information was provided to determine whether a use 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. The cases described a variety of 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).
- 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 an emergency 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 cases reported whether instructions for use/the quick start guide (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 as 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, the postmarketing safety data appear to support packaging of two devices together in one carton as a single sales unit, as is done, to maximize the likelihood that a dose is available when needed.

Additional Medication Errors

Additional medication errors were identified, which may help inform the considerations for labels and labeling for the proposed 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 a 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 the 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. 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 actively select the product off the shelf. The LCS conducted for the model DFL supported that 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.” Additionally, the name and indication of the nonprescription product will be prominently stated on the labeling to ensure lay users can 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 (i.e., 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. None of the potential users of the naloxone administered the product and all four cases were considered nonserious. Nonetheless, we plan to increase the prominence of storage information on the labeling materials as recommended by the advisory committee.

Conclusion

The assessment of device use error identified the error with the highest risk of harm is related to a potentially missed dose from users spraying naloxone outside of the patient's nostril. The Applicant's plan to co-package two nasal spray devices per carton may help to mitigate this risk.

Errors related to use of INN for the wrong indication and wrong storage were also identified. These errors may be mitigated by clear and prominent labeling displaying the product's name, indications, and storage information. The robust measures that have been undertaken to confirm the stability of this emergency product in a wide temperature range (see Section 9) will also mitigate against some potential errors related to storage of the product.

7.7.4. Limitations of Human Factors Validation Study Methodology

7.7.4.1. Pediatric Users Less Than 15 Years of Age Were Not Included in the HFVS

Background

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 ([Holland-Hall and Burstein 2016](#)). Thus, we generally recommend the HFVS include pediatric participants 10 to 17 years old.

Assessment

The Applicant states that the intended users of the proposed product include adolescents and adults. The HFVS included pediatric participants 15 to 17 years old.

Conclusion

Because pediatric users less than 15 years old were not tested, the data collected may not be generalized to the untested age range of the adolescent user group.

7.7.4.2. Two User Groups Did Not Include at Least 30% Limited Literacy Participants

Background

For HFVS in nonprescription products, we generally recommend that each distinct user group include at least 30% LL participants in the study to ensure adequate representation of the intended users.

Assessment

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.

Conclusion

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.

7.7.4.3. Participants Were Allowed an Unlimited Familiarization Period

Background

Although 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).

Assessment

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”).

Conclusion

In light of the familiarization period used in the study, the data collected does not capture the highest risk use scenario.

7.7.4.4. Moderators Employed Use of Leading Language and the “Think Aloud” Method

Background

Use of leading language might impact study participant performance and is not representative of actual use (i.e., it is unlikely someone will instruct or remind a user to use the packaging directions during actual use).

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.

Assessment

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.

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.

Conclusion

Leading language and think-aloud methods may have introduced a bias towards positive performance, which should be taken into consideration when interpreting the HFVS results.

7.7.4.5. Mock Carton Labeling Tested in the HFVS Differs From the Intend-to-Market Carton Labeling

Background

We generally expect the HFVS evaluate the intend-to-market user interface, including labels and labeling.

Assessment

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 principal display panel (PDP) include different statements, relocation of important statements, and/or changes to font size of important statements.

Conclusion

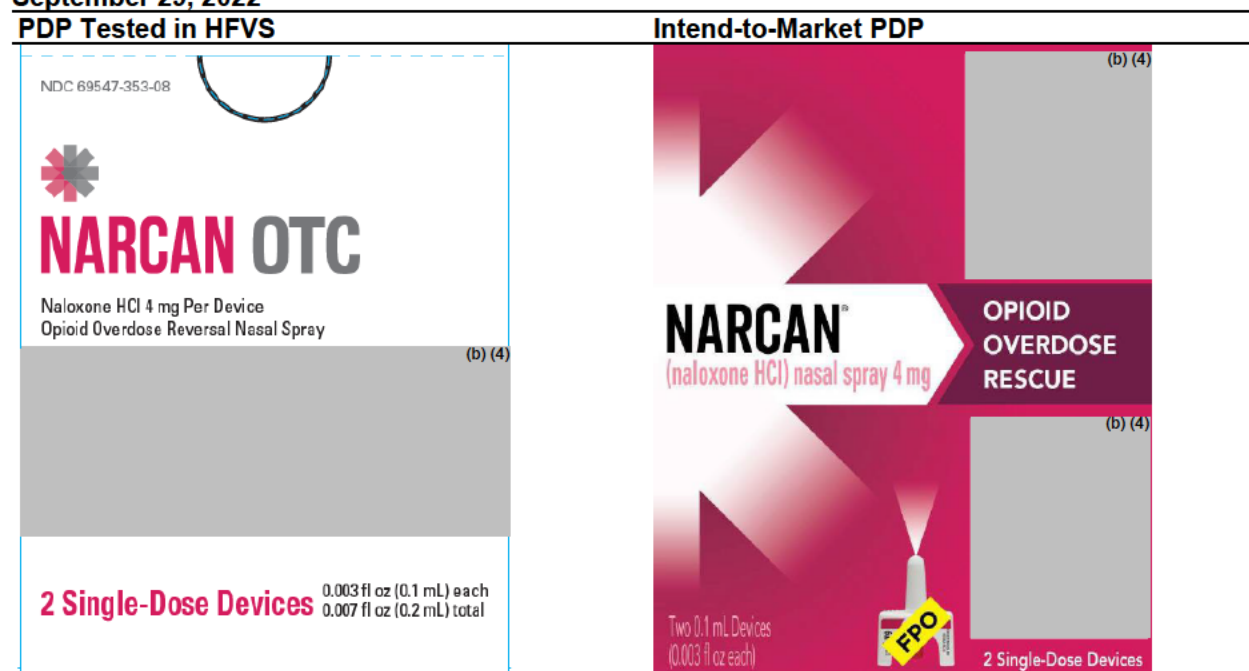
Post-validation changes to critical product labeling attributes such as formatting, layout, text size, color, etc. may impact users’ performance of critical tasks. Although it is not optimal for a flawed HFVS to be used to support safe and effective use for nonprescription naloxone, or for the Applicant to make substantial changes to the user interface and labeling materials after the HFVS was completed before marketing, the mitigations proposed to labeling based on the HFVS coupled with the potential significant public health benefit support approval of the product. Both the review team and the advisory committee carefully considered if the HFVS should be repeated with a more optimized user interface and label or if the product could move forward with a modified user interface and labeling materials without retesting. The overwhelming opinion of the advisory committee members (19:0 vote) and of the division was that the HFVS did not need to be repeated prior to approval, as long as the Applicant modified the interface and labeling as suggested.

Figure 4. 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: NDA 208411/S-006 application submitted Sept 29, 2022

Abbreviations: HFVS, human factors validation study; OTC, over-the-counter; PDP, principal display panel

Figure 5. Mock Carton PDP Tested in the HFVS Versus Intend-to-Market Carton PDP Submitted September 29, 2022

Differences reported by the Applicant:

- 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 Industry¹.
- 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: For both cartons: NDA 208411/S006 application submitted Sept 29, 2022

Abbreviations: CFR, Code of Federal Regulations; HCl, hydrochloride; HFVS, human factors validation study; OTC, over-the-counter; PDP, principal display panel

7.7.5. Qualitative Human Factors Validation Study Findings

7.7.5.1. Directions of the DFL Span Across the Back and Side Panels Contributed to Use Errors, Close Calls, and Use Difficulties

Directions of the DFL span across the back and side panels of the carton contributed to use errors, close calls, and use difficulties that may result in no dose or a delay in naloxone administration.

Background

Numerous participants experienced a user error (UE), close call, or use difficulty 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.

Assessment

UEs 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.

Conclusion

We recommend 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 to mitigate the observed use errors.

Additionally, we recommend 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 to minimize the risk of users missing steps.

7.7.5.2. Proposed User Interface Lacks an Adequate Depiction of Correct Hand and Finger Positioning

Proposed user interface lacked an adequate depiction of correct hand and finger positioning around the nasal spray, which contributed to use errors and a use difficulty that may result in no dose or a delay in naloxone administration.

Background

One participant experienced a UE where they 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 experienced a UE where they 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." Another participant experienced a difficulty when she had her thumb on the plunger but did not stabilize the top of the device while inserting into the nostril, which caused the difficulty.

Assessment

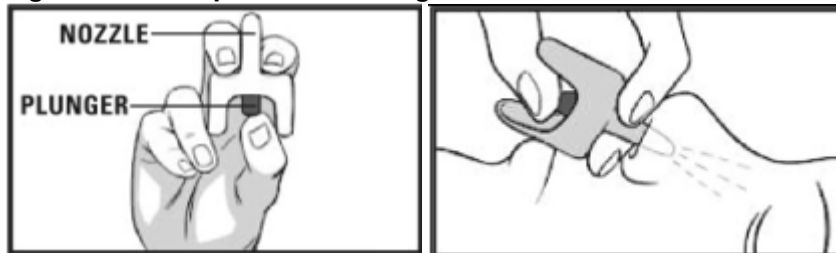
Use errors of this nature are likely to result in delayed dose or no dose of naloxone if users have difficulty activating the device, which may result in negative outcomes.

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.

Conclusion

We recommend revising the Step 2 pictogram 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: NDA 208411 original Rx label approved Dec 1, 2015

Figure 7. Nonprescription NNS DFL Step 2 Pictogram



Source: NDA 208411/S-006 application submitted Sept 29, 2022

7.7.5.3. Proposed DFL Directions on Nozzle Insertion Contributed to a Use Error

Proposed DFL Directions on nozzle insertion contributed to a UE where the participant did not keep the nozzle fully in the nostril while administering the dose, which may result in a partial dose administration.

Background

One participant did not keep the nozzle fully in the nostril while administering a dose, which resulted in a partial dose administration. The participant's subjective feedback and root cause analysis did not cite wording in the DFL as a contributing factor to the use error.

Assessment

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, our review notes 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.

Conclusion

We recommend revising the bullet to state, "INSERT the nozzle into either NOSTRIL" rather than "INSERT the tip into either NOSTRIL" may mitigate use error.

7.7.5.4. Proposed Labeling Does Not Adequately Communicate the Number of Doses Per Nasal Spray Device

Proposed labeling does not adequately communicate the number of doses in each nasal spray device.

Background

Several participants experienced a UE or close call 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."

Assessment

The user interface can be improved to further minimize the risk of this UE which if not understood may lead to patient harm.

Conclusion

We recommend 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 recommend 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.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Not applicable to this sNDA.

8.2. Extrinsic Factors

Not applicable to this sNDA.

8.3. Plans for Pediatric Drug Development

There are no plans for further pediatric development. NNS is already approved for use in all ages, including down to neonates. The Applicant intends to market its nonprescription NNS product for the same patient population.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

According to the NNS prescribing information, there are limited data on naloxone use in pregnant women and those data are not sufficient to inform a drug associated risk. However, 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 NNS doses) based on body surface area comparison.

There is also 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.

9. Product Quality

9.1. Device or Combination Product Considerations

The drug product solution is presented in a 125 μ L(0.125 mL) type I borosilicate glass vial (fulfills the requirements of the United States Pharmacopeia) closed with a chlorobutyl rubber plunger (container closure system), which in turn is mounted into a unit-dose nonpressurized

nasal spray device and container holder assembly. When the device is actuated the cannula of the actuator will puncture the septum on the vial stopper and deliver a 100 µL (0.1 mL) spray of the naloxone intranasal solution. There is no priming required before use and that the device can be used in any orientation. See Section [13.3](#) for more information on the device including [Figure 10](#).

In summary, this prescription to nonprescription switch is proposed without any changes to the approved Narcan 4 mg nasal spray device presentation. The currently available safety and efficacy data regarding device observations and/or malfunctions demonstrates the switch will not impact the ability of the device to achieve its intended use.

9.2. Summary

This prescription-to-nonprescription switch is proposed without any changes to the approved Narcan 4 mg drug product presentation. The proposed nonprescription product will have the same drug substance, drug product formulation, nasal spray device, drug product manufacturing process, and expiry as the current prescription product. It is important to document that there were several chemistry, manufacturing, and controls (CMC) supplements after the initial NDA approval in 2015, some of which are related to the postmarketing requirements (PMRs) and postmarketing commitments (PMCs) issued to ensure product quality related to product stability and reliability. All PMRs/PMCs have been fulfilled and deemed adequate by CMC. According to our combination product review staff from CDRH, from a device perspective, the switch from prescription to nonprescription is supportable as there are no changes to the device constituent, specifications, manufacturing, or control strategy. The CDRH reviewers noted that this product is for emergency-use and should perform to a 99.999% reliability. Additionally, the proposed switch to nonprescription status is acceptable from a CMC perspective and there are no significant concerns for the nonprescription product's drug stability.

9.3. Drug

See Section [13.4](#).

9.4. Drug Formulation

The proposed nonprescription NNS drug formulation is qualitatively and quantitatively the same as the prescription formulation; however, the formulation did change since the original approval of NNS. The nonprescription formulation is composed of the active pharmaceutical ingredient naloxone (40 mg/mL) and four excipients (not including water). Each nasal spray device will deliver 4 mg of naloxone hydrochloride solution in a delivery volume of 100 µL (0.1 mL).

There was a single change in drug formulation after initial approval. The original approval was based on a formulation (b) (4). The approval of S-002 changed the final formulation (GEN2) (b) (4).



The composition of the nonprescription product otherwise remained unchanged as seen in Tables [13](#) and [14](#).

9.5. Relevant Regulatory History

The following information about the product was noted in Dr. Joshua Lloyd's cross discipline team leader summary approval review dated November 18, 2015 (DARRTS Reference ID: 3848571), in which he stated:

“The naloxone API is supplied by (b) (4) (DMF (b) (4)). The drug product is formulated in (b) (4) comprising the following excipients: sodium chloride, disodium edetate, and benzalkonium chloride, in a concentration of 40 mg/ml. The container closure system is a glass vial with a chlorobutyl stopper, which is then encased within a nasal actuator and container holder. The nasal spray device is by Aptar, under DMF (b) (4) and has been reviewed by CDRH and OPQ, for use with the naloxone drug product. Each unit dose device, formulated to deliver one dose of naloxone, is placed within a blister package. Two units or blister packages are then stored per carton. Adequate data to assess the device delivery of the drug product and to assure the identity, strength, purity, and quality of the drug product is provided. The drug product is granted an expiry of 24 months, when stored at room temperature.”

Dr. Lloyd then went on to state, “there are no significant, outstanding manufacturing process risks” and “no significant, outstanding microbiological risks that prevent approval of this application.” He did acknowledge several concerns that could be addressed postapproval with PMRs/PMCs that include the following:

1. Establish reliability requirements of the combination product and complete testing which verifies the combination product reliability (PMR 2990-1).
2. Establish procedures for monitoring reports of failures of the combination product to activate or fail to deliver the full-labeled dose (PMR 2990-02).
3. Perform a leachable safety study for the (b) (4) used in the container closure system (PMC 2990-03).
4. Perform a long-term stability evaluation of at least three manufactured lots of the combination product needed to be conducted at the following temperatures a) 2 °C to 8°C and b) 40 °C/75% RH - to extend the time points out to 24 months (PMC 2990-4).

Although all four PMR/PMCs that were requested at the time of NNS approval were fulfilled over subsequent years, it is important to document the data that supported the resolution of the PMR/PMCs so that we can be assured of the reliability and stability of the product. The fulfillment of these PMR/PMCs adequately address any residual concerns related to “failure to deliver a dose” or “failure to follow storage conditions” that occurred infrequently as reported in the postmarketing data.

Device Reliability and Monitoring for Reports of Failures

Dr. Lloyd noted a concern by Ryan McGowan, a biomedical engineer in the Center for Devices and Radiological Health (CDRH), who performed the initial review for the device. At the time of approval, Mr. McGowan stated,

“Device constituent parts of the combination product have been designed appropriately for the product’s intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture.” However, Mr. McGowan thought that the application contained inadequate information to demonstrate that the manufactured product was able to activate reliably after exposure to a variety of real-world conditions and as a result there could be a potential for under-dosing or failure-to dose events. Specifically, he was concerned about dose content uniformity, which allowed for relatively wide batch release specifications. The specification required that (b) (4)

Given the relatively wide safety margin with naloxone, there is little concern for the upper limits of these release specifications, particularly since Narcan is labeled with dosing recommendations up to a total of 10 mg of naloxone. In general, the greatest concern would be for releasing a batch that might not deliver an adequate dose of naloxone in an immediately life-threatening situation. However, given the pharmacokinetic profile of this product which achieves much higher systemic exposures to naloxone than the approved comparator dose of naloxone (i.e., 0.4 mg IM), the lower limit of these specifications is also acceptable.”

Fulfillment of PMRs 2990-1 and 2990-2 that dealt with the combination product’s reliability, was evaluated by John McMichael and Alan Stevens from CDRH Combination Products Team who wrote in an intercenter memorandum dated July 12, 2018 (DARRTS Reference ID: 4376777) that they had interacted with the Applicant to develop a protocol for the reliability of the device as well as a monitoring plan over time. They evaluated interim and final reports and performed root cause analyses. They stated in their executive summary:

“A study to evaluate the reliability of the NNS 4 mg device was initiated. . . . The reliability study was conducted in two parts. (b) (4)

(b) (4)

(b) (4)

Once these observations and calculations were made, it was important to bridge the new GEN2 formulation to the old formulation. Rumi Young and Alan Stevens from CDRH stated in an intercenter memorandum dated September 27, 2018 (DARRTS Reference ID: 4376785) that the container closure system for the GEN2 formulation is identical to the previous commercial container closure system (b) (4) They did identify a risk (b) (4)

although the risk was thought to be low (b) (4)

The Applicant provided a detailed study (b) (4)

The study was done with the GEN2 nasal spray device, which consists of the formulation change (b) (4) and was deemed adequate. PMRs 2990-1 and 2990-2 were fulfilled on October 3, 2018.

In an intercenter consult memorandum dated January 19, 2023 (DARRTS Reference ID: 5123889), Courtney Evans and Alan Stevens from CDRH stated, “from a device perspective, the switch from Rx to NonRx is supportable as there are no changes to the device constituent, specifications, manufacturing, or control strategy. It is difficult to assess potential for device failures based on an NonRx designation; however, this product is emergency-use and should perform to a 99.999% reliability. At this time, there are minimal reports of device failures and/or malfunctions regarding NNS.”

Product Stability Including Product Expiry

To further verify the products stability the Applicant was asked to conduct a long-term stability evaluation under PMC 2990-4 placing at least three manufactured lots of NNS, 40 mg/mL, on long-term stability evaluation at the following temperatures:

- a. 2 to 8 °C
- b. 40 °C/75% relative humidity (RH) - to extend the time points out to 24 months

Rumi Young and Alan Stevens from CDRH stated in an intercenter memorandum dated September 27, 2018 (DARRTS Reference ID: 4376785), that the Applicant provided data (b) (4)

They stated that along with the 24 months of stability at accelerated conditions filed as part of PMR 2990-4, (b) (4)

In her summary review for regulatory action on S-002 dated September 23, 2019 (DARRTS Reference ID: 4495710), Dr. Sharon Hertz stated that the initial response to conducting long-term stability evaluation of NNS at exaggerated temperatures was inadequate and issued a Complete Response (CR) on March 4, 2019. (b) (4)

. The initial CR was based on the CMC review by Dr. Venkateswara Pavuluri

NDA 208411/S-006

Narcan (naloxone hydrochloride) nasal spray, 4 mg

dated November 8, 2018 (DARRTS Reference ID: 4347804), where she stated that the final report did not support (b) (4)

Data were (b) (4)
provided for long-term storage for up to 24 months below 40 °C. She stated,

(b) (4)

Dr. Pavuluri also stated that the Applicant had not adequately addressed (b) (4)

(b) (4)

The CR listed the following requests to the Applicant:

(b) (4)

All requests under PMC 2990-4 were considered fulfilled on April 11, 2019 (DARRTS Reference ID: 4417853). The GEN2 product was demonstrated to be stable from 2 °C to 8 °C and 40 °C/75% RH - to extend the time points out to 24 months.

On April 15, 2020, S-004 was received to the NDA that provided for the extension of shelf life of the GEN2 product from 24 months to 36 months. This data was reviewed by FDA CMC reviewer Dr. Daneli Lopez-Perez, and the 36-month expiry was documented in an Office of Lifecycle Drug Products review dated July 22, 2020.

Extractable and Leachable Assessment

The initial leachable safety study for the (b) (4) used in the container closure system under PMC 2990-03 was considered fulfilled on October 18, 2018 (DARRTS Reference ID: 4342083). The approval of the current GEN2 formulation in S-002 resulted in PMR 3707-1 to look for extractables and leachables of the new presentation included the (b) (4) and the GEN2 formulation (b) (4). The Applicant provided a response to the PMR on July 30, 2020. In the cover letter of the PMR response, the Applicant notified FDA (b) (4).

(b) (4) and that a new extractable assessment would be provided in the annual report. The (b) (4) for the device would still be supplied by Aptar under drug master file (DMF) (b) (4). The extractable study was submitted to FDA in Annual Report 6 on January 13, 2022. Extracts from the device components (b) (4) were analyzed by headspace gas chromatography/mass spectroscopy for volatile extractables, gas chromatography/mass spectroscopy for semi-volatile extractables, and LC-MS for nonvolatile extractables. No extractables were observed above the specified analytical evaluation threshold based on a maximum potential exposure of the user to (b) (4) µg/day and (b) (4) µg/day. The (b) (4)

(b) (4) is a minimal risk to the drug product quality. Emergent Operations Ireland Ltd. claims a categorical exclusion for S-006 in accordance with 21 CFR 25.31(a).

From a CMC perspective, the proposed switch to nonprescription is acceptable and there are no significant concerns for the nonprescription product's device reliability or drug stability. Additional details to the CMC evaluation can be found in a drug product assessment dated February 13, 2023, in Panorama and Section [13](#).

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Not applicable to this sNDA.

11. Advisory Committee Summary

As this application for NNS represents a potential first-in-class product in a new therapeutic category for nonprescription drugs, the application was discussed at a joint meeting of the Nonprescription Drugs Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee on February 15, 2023. The focus of the meeting was on the adequacy of the data supporting NNS' nonprescription application. The panel considered the established efficacy of NNS, the available postmarketing safety data for INN, and the data supporting NNS' nonprescription user interface from both the pivotal LCS conducted for FDA as well as the HFVS conducted by the Applicant. The advisory committee panel overwhelmingly voted in favor that the benefit-risk profile of NNS supported its switch to nonprescription use by a vote of

19-0. They acknowledged that the HFVS was flawed but felt that the benefit of naloxone to those with opioid overdose outweighed the imperfections in the trial design of the HFVS. They believed that the labeling materials could be further optimized based on the findings of the HFVS and that this would improve the ability of consumers to use the product effectively.

Most panelists found the overall benefit-risk profile of naloxone to be a critical factor in their decision-making. Because opioid overdose is a life-threatening condition and because the possibility of saving a life with naloxone overshadows both common and serious adverse events, they expressed that the benefit-risk profile heavily favored NNS's benefit. The potential positive public health impact of a nonprescription naloxone product to save lives was a compelling reason cited by many panelists. This sentiment was reiterated by the six speakers during the Open Public Hearing.

The panelists noted that FDA's model naloxone DFL, upon which the proposed DFL for NNS is based, as well as its LCS results were adequate and supportive of its nonprescription use, and they did not make suggestions regarding the product-specific wording. The panel aligned with FDA that the presentation of the IFU over two panels that were evaluated in the HFVS were not ideal. They also had concerns that there was no QSG like the prescription product had in each blister pack in case the blister pack was separated from the carton. They questioned the pictograms that showed the hand placement of the device and thought that the pictogram showing hand placement that accompanied the prescription product was more informative.

The panel believed that various mitigations to improve labeling would strengthen the safety and efficacy of the product in consumers' hands. Mitigations suggested included changes in the labeling language on the PDP, inclusion of additional device diagrams, improved pictograms illustrating the correct hand position to use the device, addition of a QSG in each blister pack that reiterated the DFL IFU, and improved positioning of the IFU information on the carton. The panel made several suggestions for the labeling that could improve the user interface and did not consider a repeat HFVS necessary to validate those changes before approval.

For a detailed summary of advisory committee discussions, refer to the official meeting minutes and transcript.

III. Additional Analyses and Information

12. Summary of Regulatory History

Prior to the submission of investigational new drug (IND) 130200 or new drug application (NDA) 208411 for the consideration of switching Narcan nasal spray (NNS) from prescription to nonprescription status, there was a long history of efforts to increase naloxone access to the community that had impact on FDA policy. Those efforts will be summarized in this section as well as the history of this application.

12.1. Efforts to Increase Access to Naloxone

- **2012 Naloxone workshop.** A workshop was sponsored by FDA, Centers for Disease Control and Prevention, National Institute on Drug Abuse, and the Office of the Assistant Secretary for Health and Human Services to discuss expanding access to naloxone in the community. At this time the approved formulations of naloxone were all injectable used primarily by medical professionals. FDA was encouraged to expand access to naloxone by approving a noninjectable form of naloxone for community use.
- **NDA 208411 Narcan (naloxone hydrochloride 4 mg) nasal spray approved** on a priority basis as a prescription community use product for the emergency treatment of known or suspected opioid overdose on November 18, 2015
- **Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee on October 5, 2016.** At this meeting, there was discussion about the pharmacokinetic (PK) standard for approval of novel naloxone products intended for use in the community. There was other topics discussed including naloxone dosing in pediatric patients and whether there should be different doses of naloxone available for use in the community setting.
- **Five-Point Strategy to Combat the Opioid Crisis Health and Human Services in 2018** ([U.S. Department of Health and Human Services 2018](#)). The Department of Health and Human Services announced its strategy to combat the Opioid Crisis, which includes prevention, treatment, and recovery services including expanding access to opioid overdose reversal treatments such as naloxone with a focus on high-risk populations. This strategy was unveiled by President Trump, who called for the ongoing opioid epidemic to be declared as a nationwide public-health emergency ([Haffajee and Frank 2018](#)).
- **Second Joint Advisory Committee meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee was held December 17 to 18, 2018.** Topics discussed included ways in which FDA could increase the availability of naloxone products intended for use outside of the health care setting.
- **Federal Register Notice (84 FR 8728) was published March 2019.** As part of a wide governmental effort to address the national crisis of opioid overdose deaths, the Agency has identified broader availability of naloxone, including potential nonprescription availability,

as one means to help reduce overdose deaths. Some stakeholders have identified the need to perform these studies as a barrier to development of a nonprescription naloxone drug product. To help address this concern, FDA developed a model drug facts label (DFL) for a potential nonprescription naloxone drug product. The model DFL is intended to contain adequate information (except for individual device-specific information, such as how to use a particular injector or spray device, which would be added by the product sponsor) that a consumer would need to administer naloxone safely and effectively for its intended use in the nonprescription setting.

- **The Reagan-Udall Foundation for the FDA held a virtual public meeting entitled “Naloxone Access: Answering Questions” on March 29, 2022.** This virtual public meeting explored some of the most frequently asked questions about access to naloxone. Stakeholders included harm reduction specialists, physicians, pharmacists, and regulators who shared their experiences in addressing the availability of naloxone treatment for heroin, fentanyl, and prescription opioid overdose.
- **The Reagan-Udall Foundation for the FDA held a virtual roundtable discussion by invitation-only on October 25, 2022.** This virtual roundtable was attended by a variety of public and private payor representatives and experts to discuss the economic implications of some naloxone products transitioning from prescription to nonprescription status.
- **Federal Register Notice (87 FR 68702) was published on November 16, 2022.** This FR notice was entitled “Safety and Effectiveness of Certain Naloxone Hydrochloride Drug Products for Nonprescription Use.” It announced FDA’s “preliminary assessment that certain types of naloxone hydrochloride (“naloxone”) drug products may be approvable as safe and effective for nonprescription use including naloxone nasal spray up to 4 mg, naloxone autoinjector for IM or subcutaneous use up to 2 mg and have the potential to be safe and effective for use as directed in nonprescription drug labeling without the supervision of a healthcare practitioner.” Development of Nonprescription Narcan (naloxone hydrochloride) nasal spray

12.2. Development of Nonprescription NNS

- **April 25, 2016 – Initial pre-IND type B meeting** held under pre-IND 130200: Adapt Pharma Operations Limited (Adapt) met with FDA to discuss the requirements and key labeling considerations (b) (4). FDA suggested that a meaningful difference needed to be proposed to justify prescription and nonprescription marketing statuses for two strengths of the same product. FDA also provided responses to questions regarding human factors (HF) data and suggested an overall approach to the DFL on June 3, 2016.
- **February 27, 2017 – A pre-IND type B meeting** took place to discuss plans to change marketing status of the 4 mg strength from prescription to nonprescription while retaining prescription marketing status for the 2 mg strength. Label comprehension testing was also discussed. FDA reiterated the need for a meaningful difference to justify prescription and nonprescription status at the same time and provided additional suggestions to the DFL and label comprehension studies on March 28, 2017.

- **May 9, 2019 – Type B meeting** was conducted to discuss plans for marketing naloxone as both a nonprescription and prescription product. Applicant was informed that it was up to them to propose a full versus partial prescription to nonprescription (Rx-to-NonRx) switch but that they would need to justify their request. FDA would decide on the adequacy of the justification during a formal review after an application submission.
- **October 6, 2020 – Type C meeting** was held to discuss its proposed self-selection and label comprehension study design to maintain both nonprescription and prescription use of the product. FDA did not agree that there was a clinically meaningful difference between the patient populations described but did maintain that the business decision to pursue a full versus partial Rx-to-NonRx switch remained with the Applicant.

12.3. Development of the Human Factors Program

We previously reviewed the results of the human factors validation study (HFVS) for the Rx NNS under NDA 208411. Our review concluded that the HFVS results supported safe and effective use of the then proposed Rx NNS user interface by the intended users in the intended use environments.

As communicated in *Federal Register* Notice of March 11, 2019 (84 FR 8728) and within this review, FDA developed two versions of a model naloxone DFL (one for nasal spray and one for autoinjector) supported by a Comprehension for OTC Naloxone (CONFER) pivotal label comprehension study to encourage naloxone sponsors to enter the nonprescription market and increase access to naloxone. The FDA model DFL directions include placeholders (e.g., image of device and Step 2 instructions on how to give a dose) that would need to be replaced with device-specific information. If an Applicant elects to use the model DFL, the device-specific instructions may be added and evaluated in a simulated HFVS designed to evaluate whether the user interface can be used safely and effectively by intended users for the intended use under the expected environment(s) of use.

- On April 25, 2016, during the pre-IND meeting with the Applicant under IND 130200, we provided responses to questions regarding HF data/information needed to support the proposed market conversion from prescription to nonprescription.
- On February 27, 2017, during the Type B meeting with the Applicant under IND 130200, we provided a response to a question regarding HF data/information needed to support the proposed market conversion from prescription to nonprescription.
- On May 9, 2019, during the Type B End of Phase 2 Meeting with the Applicant under IND 130200, we provided a response to a question regarding the Applicant's proposal to leverage label comprehension data from the model DFL. We responded that the Applicant needs to validate the proposed DFL in a HF study. We recommended the Applicant conduct a comprehensive use-related risk analysis to inform the design of the HFVS protocol. We recommended the Applicant submit the HFVS protocol for feedback before commencing the study.

- On September 29, 2022, the Applicant submitted NDA 208411/S-006 to seek approval for the full prescription to nonprescription switch of NNS, 4 mg, which included the results of a simulated-use HFVS.

The Applicant did not submit the HFVS protocol for review prior to conducting the HFVS study to support the proposed market conversion from prescription to nonprescription.

In the HFVS, the Applicant reported study results as correct, acceptable, or incorrect using quantitative thresholds for success (e.g., percentage acceptable). However, generally HFVS's are not intended to provide quantitative information on primary, secondary, or composite outcomes.³ The results of these studies should be analyzed qualitatively, using information gathered from every occurrence of use error,⁴ use difficulty,⁵ and close call.⁶ 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 use difficulty and close calls 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.⁷

12.4. Pediatric Assessment

The regulatory history and basis for pediatric approval for prescription NNS is provided in a high-level summary under Section [6.3.1](#). and in greater detail in Dr. Ndidi Nwokorie's Division of Pediatrics and Maternal Health memorandum dated January 30, 2023 (DARRTS Reference ID: 5117174). As stated there, no new pediatric efficacy or PK data were required for the original approval of NNS. The Applicant leveraged efficacy data for previously approved Narcan for injection to support the pediatric approval of NNS. The Applicant also provided information from available publications to support safety of the nasal spray product in pediatrics. During the original review, some concerns had been raised as to whether the actuator tip may be properly positioned in pediatric patients under five years of age due to nasal developmental differences between young children and adults, whether a single 4 mg intranasal (IN) dose of naloxone could

³ 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. See the FDA Draft Guidance for Industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016)..

⁴ 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.

⁵ A use difficulty is defined as a difficulty, or struggle, encountered during use, which is typically momentary and overcome by the user.

⁶ 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.

⁷ This section is attributed to Barbara Cohen who wrote this summary of the model DFL development for the Advisory Committee Backgrounder.

result in higher-than-expected exposures in pediatric patients, and whether IN instrumentation in the youngest patients could induce respiratory distress due to obligate nasal breathing. These concerns were outweighed by the urgent need for a community use product for children. FDA approved NNS to ensure the availability of naloxone to provide a life-saving therapeutic option in the full pediatric age range for emergency use in the community setting. Concerns about pediatric safety were addressed by FDA's issuing a postmarketing requirement (PMR) for the Applicant to submit information from a postmarketing monitoring program for the detection and evaluation of underdose and failure-to-dose events. An interim report was submitted February 27, 2017, and was considered adequate to fulfill the PMR without evidence of significant pediatric safety concerns.

The Applicant intends to market its nonprescription NNS product with the same active ingredient, indication, dosage form, dosing regimen, and route of administration as the currently approved prescription-only product. Therefore, its application is exempt from requirements under the Pediatric Research Equity Act (21 U.S.C. 355c).

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Not applicable.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Not applicable.

13.3. Executive Summary

13.3.1. Introduction

The Applicant, Emergent Operations Ireland Limited (Emergent LTD), submitted supplement-006 for the full prescription-to-nonprescription (Rx-to-nonprescription) switch of NNS, 4 mg configuration. NDA 208411 also supported approval of a 2 mg configuration of NNS, but it has never been launched. The Applicant plans to voluntarily withdraw the 2 mg configuration prior to the approval of the nonprescription product.

The drug product is indicated for the treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. The intended patient population is adults and children, including neonates.

13.3.2. Brief Discussion of Nonclinical Findings

No new pharmacology or toxicology information was submitted to this NDA supplement, nor was nonclinical information required. There were no nonclinical findings of concern for the proposed Rx-to-nonprescription switch. See Section [13.13](#) for additional information.

From the nonclinical perspective, supplement-006 for nonprescription NNS is approvable.

13.3.3. Recommendations

Approvability

Approvable from the nonclinical perspective.

13.3.4. Additional Nonclinical Recommendations

None.

13.3.5. Labeling

Not applicable.

13.4. Drug Information

13.4.1. Drug

CAS Registry Number (Optional)

51481-60-8

Generic Name

Naloxone hydrochloride

Code Name

N/A

Chemical Name

(b) (4)

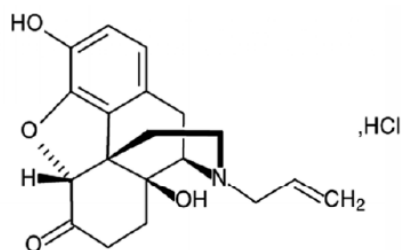
Molecular Formula/Molecular Weight

C₁₉H₂₁NO₄ • HCl (b) (4)

NDA 208411/S-006

Narcan (naloxone hydrochloride) nasal spray, 4 mg

Figure 8. Structure or Biochemical Description



Source: Kim, S, J Chen, T Cheng, A Gindulyte, J He, S He, Q Li, BA Shoemaker, PA Thiessen, B Yu, L Zaslavsky, J Zhang, and EE Bolton, 2022, PubChem 2023 update, Nucleic Acids Research, 51(D1): D1373-D1380.

Pharmacologic Class

Opioid antagonist (established pharmacological class)

13.4.2. Relevant INDs, NDAs, BLAs and DMFs

Tables [11](#) and [12](#) show relevant information submitted to FDA.

Table 11. Relevant INDs and NDAs

Information	Strength (Route)	Marketing Status	Sponsor/Applicant
NDA 016636 Narcan (naloxone HCl) injection	1 mg/mL (IV, IM, SC)	Withdrawn, FR effective	Adapt Pharma (formerly Endo)
IND 114704 Narcan (naloxone HCl) injection	Investigational doses (IV, IM, SC)	Not applicable	Adapt Pharma (formerly Endo)

Source: Reviewer generated table of DARRTS and nonclinical review of NDA 208411 Reference ID: 3841831

Abbreviations: FR, Federal Register; HCl, hydrochloride; IM, intramuscular; IND, investigational new drug; IV, intravenous; NDA, new drug application; SC, subcutaneous

Table 12. Relevant DMFs

DMF	Subject of DMF	Holder	LOA Filing Date
(b) (4)			

Source: Reviewer generated table of DARRTS entries under DMFs as cited above and NDA 208411

Abbreviations: DMF, drug master file; HCl, hydrochloride; LOA, Letter of Authorization; USP, United States Pharmacopeia

13.5. Drug Formulation

The proposed nonprescription NNS drug formulation is qualitatively and quantitatively the same as the prescription formulation. The nonprescription formulation is comprised of the active pharmaceutical ingredient naloxone (40 mg/mL) and four excipients (not including water). Each nasal spray device will deliver 4 mg of naloxone hydrochloride solution in a delivery volume of 100 μ L (0.1 mL).

Table 13. Quantitative Composition of the Nonprescription Formulation

Component	Quality Standard	Function	Strength: 40 mg/ml	
			Quantity per ml	Quantity per dose (100 µL)
Naloxone HCl (b) (4) (corresponding to naloxone HCl)	USP, Ph. Eur	Active ingredient		(b) (4)
			(40.0 mg)	(4.0 mg)
Benzalkonium Chloride (b) (4)	USP, Ph. Eur	Preservative	(b) (4)	
Disodium Edetate	USP, Ph. Eur	Stabilizer		
Sodium Chloride	USP, Ph. Eur	(b) (4)		
Hydrochloric Acid (b) (4)	USP/NF, Ph. Eur			
Water (b) (4)	USP, Ph. Eur			

Source: Applicant's excerpted table NDA 208411

Abbreviations: HCl, hydrochloride (b) (4) USP, United States Pharmacopeia; WFI, water for injection

Table 14. Quantitative Composition of the Prescription Formulation

Concentration		40 mg/mL	
Component	Grade	Quantity per mL	Quantity per unit dose (100 µL)
Naloxone HCl (b) (4) (corresponding to naloxone HCl)	USP	(40.0 mg)	(4.0 mg)
Benzalkonium chloride (b) (4) % v/v	USP	(b) (4)	
Disodium edetate	USP		
Sodium chloride	USP		
Hydrochloric acid, dilute	USP		
Purified water	USP		

USP = United States Pharmacopeia

(b) (4)

Source: Applicant's excerpted table NDA 208411

See Section [13.13](#) for information about the device.

13.5.1. Comments on Novel Excipients

There are no novel excipients in the proposed nonprescription NNS formulation. All the proposed excipients were used in the prescription version of the drug product and the level of each excipient is unchanged (Tables [13](#) and [14](#)).

13.5.2. Comments on Impurities/Degradants of Concern

There are no drug substance impurities of concern. For additional details regarding impurities and degradants, refer to the chemistry, manufacturing, and controls (CMC) review for NDA 208411 in Panorama.

13.5.3. Proposed Clinical Population and Dosing Regimen

Each nasal spray device will deliver 4 mg of naloxone hydrochloride solution in a delivery volume of 100 μ L (0.1 mL). The proposed dose is one spray (4 mg/0.1mL); however, additional doses may be administered to alternating nostrils every 2 minutes. For the toxicological safety assessment, a reference dose of 8 mg/day (two sprays) will be considered the reference maximum daily human dose.

The dosing population includes adults and children (including neonates).

13.5.4. Regulatory Background

Naloxone hydrochloride was originally approved as Narcan injection (NDA 016636, wholly owned by Endo Laboratories [Endo]) in 1971 for the treatment of known or suspected narcotic overdose. The original approval allowed for the administration of Narcan injection through the intravenous (IV), intramuscular (IM), and subcutaneous (SC) routes of administration. According to the original Narcan injection product label, the reference dose was 0.4 mg to (b) (4) mg, which could be administered repeatedly at 2-to-3-minute intervals until the desired degree of opioid antagonism was obtained.

NNS was approved for prescription intranasal use on November 18, 2015, under NDA 208411. It was indicated for the treatment of known or suspected narcotic overdose in adults and children (4 mg/day).

On January 24, 2017, a 2 mg dosage strength of NNS was approved under S-001, with an identical CCS as reviewed by nonclinical reviewer Carlic Huynh, PhD, December 20, 2016, (DARRTS Reference ID: 4031361). The 2-mg configuration was never launched (Applicant's Cover Letter under supplement-006). Further, the Cover Letter for supplement-006 states that Emergent proposes to only market the Narcan 4 mg configuration as a nonprescription product. On February 10, 2023, *Federal Register* Notice (88 FR 8873) announced that the Applicant was voluntarily withdrawing their product NNS, 2 milligrams/0.1 milliliter.

CMC prior approval supplement NDA 208411 S-002 was submitted to the agency on June 8, 2018, to implement a new product formulation (GEN2) (b) (4)

(b) (4) At that time the Applicant proposed a container-closure change to distinguish the GEN2 formulation from the currently marketed formulation.

On March 4, 2019, a Complete Response was issued to the supplement (DARRTS Reference ID: 439327). On September 23, 2019, the supplement was approved (DARRTS Reference ID: 4495636). The changes included a second generation (“GEN2”) formulation (b) (4) and a change to the secondary container closure system (CCS). (b) (4)

(b) (4) as shown in [Figure 9](#). PMR 3707-1 was issued as a result to conduct an extractables and leachables assessment using the (b) (4) and the GEN22 formulation to determine if any volatile compounds could be released. According to nonclinical review by Dr. Carlic Huynh, PhD, on August 20, 2019 (DARRTS Reference ID: 4479196), and the approval letter with PMR notification submitted September 23, 2019 (DARRTS Reference ID: 4495636) PMR 3707-1 was fulfilled on March 8, 2023 (DARRTS Reference ID: 5137813) based on results from an extraction study determined to be valid by the Office of Product Quality. See Section [13.13](#) for current information on the CCS.

Figure 9. Change (b) (4) for the 4 mg Presentation (b) (4)



Source: Applicant's figures from supplement-002

13.6. Studies Submitted

13.6.1. Studies Reviewed

No new nonclinical toxicology studies were submitted with S-006 or required for the proposed prescription-to-nonprescription switch.

To support the safety of the prescription NNS, the Applicant relied upon published literature information of the known pharmacology and toxicology for naloxone, and FDA's finding of safety for NDA 016636 (Narcan [naloxone hydrochloride (HCl)] injection).

Whenever necessary, a summary of the available data reviewed for the prescription intranasal drug product as well as pertinent information included on the prescription labels for Narcan (naloxone HCl) injection (NDA 016636) and NNS (NDA 208411) is provided below ([Table 15](#)).

Table 15. Sources of Pharmacological and Toxicological Information Reviewed

Source	Date of Submission/Latest Revision Date
Pharmacology and toxicology NDA review for prescription Narcan (naloxone HCl) nasal spray (NDA 208411)	Submitted to DARRTS 11/2/2015
Prescription label for Narcan (naloxone HCl) injection	Latest revision 2003
Prescription label for Narcan (naloxone HCl) injection	Latest revision 8/2022

Source: Pharmacology and Toxicology NDA Review, primary reviewer Chibueze Ihunnah
Abbreviations: HCl, hydrochloride; NDA, new drug application

13.6.2. Studies Not Reviewed

None.

13.6.3. Previous Reviews Referenced

Table 16. Previous Reviews Referenced

NDA	Date of Approval	Drug Product	Reviewer/Division	Discipline	Date Submitted to DARRTS
208411	11/18/2015	Narcan (naloxone HCl) nasal spray (4 mg)	Newton H. Woo, PhD / formerly in the DAAAP	P/T	11/2/2015
208411/ S-001	1/24/2017	Narcan (naloxone HCl) nasal spray (2 mg)	Carlic K. Huynh, PhD/ formerly in the DAAAP	P/T	12/20/2016
208411/ S-002	9/23/2019	Narcan (naloxone HCl) nasal spray (2 mg)	Carlic K. Huynh, PhD/ formerly in the DAAAP	P/T	8/19/2019
208411/ S-006	Not approved at the time of review	Narcan (naloxone HCl) nasal spray	Chibueze A. Ihunnah, PhD / ONPD	P/T	11/23/2022

Source: Pharmacology and Toxicology NDA Review, primary reviewer Chibueze Ihunnah
Abbreviations: DAAAP, Division of Anesthesia, Analgesia, and Addiction Products; ONPD, Office of Nonprescription Drugs; P/T, pharmacology toxicology

13.7. Pharmacology

13.7.1. Primary Pharmacology

No new pharmacology studies with intranasal naloxone (INN) were submitted nor required for this application.

For supplement-006, the Applicant is partly relying upon FDA's finding of safety for NDA 016636 (Narcan [naloxone HCl] injection). This is the same approach employed by the Applicant for the approval of Rx NNS (NDA 208411). An excerpt from the Rx label for Narcan (naloxone HCl) injection regarding primary pharmacology is provided below:

NARCAN prevents or reverses the effects of opioids including respiratory depression, sedation, and hypotension. Also, NARCAN can reverse the

psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine. NARCAN is an essentially pure opioid antagonist, i.e., it does not possess the “agonistic” or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

NARCAN has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of physical dependence on opioids, NARCAN will produce withdrawal symptoms. However, in the presence of opioid dependence, opiate withdrawal symptoms may appear within minutes of NARCAN administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of NARCAN and to the degree and type of opioid dependence.

The mechanism of action is described further on the label for Narcan (naloxone HCl) nasal spray (NDA 208411):

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.

13.7.2. Secondary Pharmacology

No new secondary pharmacology studies with INN were submitted nor required for this application. An excerpt from the pharmacology toxicology review for prescription Narcan (naloxone HCl) nasal spray regarding secondary pharmacology is provided below (DARRTS Reference ID: 3841831):

Naloxone has been reported to influence pharmacological responses to a variety of non-opioid drugs by antagonizing the secondary effects with some effects unrelated to the direct occupation of opioid receptors. For example, naloxone at high doses appears to act as an antagonist at the gamma aminobutyric acid receptor and has been implicated in the convulsant properties associated with high doses in mice ([Dingledine et al. 1978](#); [Svensson et al. 2000](#)). A dose of approximately 150 mg/kg of naloxone administered to mice intraperitoneally produced convulsions in approximately 10% of animals injected ([Dingledine et al. 1978](#)), which corresponds to HED of 731 mg for a 60 kg person.

13.7.3. Safety Pharmacology

No new safety pharmacology studies with INN were submitted nor required for this application.

13.8. Pharmacokinetics/ADME/Toxicokinetics

13.8.1. PK/ADME

No new PK/ADME studies with INN were submitted nor required for this application.

An excerpt from the Rx label for Narcan (naloxone HCl) nasal spray (NDA 208411) regarding PK/ADME is provided below. See the Rx label for additional information.

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 IM routes of administration. The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride.

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 NNS (2 mg or 4-mg dose of naloxone hydrochloride), the mean plasma half-life of naloxone in healthy adults was approximately 1.85 (33% coefficient of variation [CV]) hours and 2.08 (30% CV) hours; respectively, which was longer than that observed after administrations of a 0.4 mg naloxone hydrochloride IM injection, where the half-life was 1.24 hours (26% CV). In a neonatal study of naloxone hydrochloride injection, the mean ($\pm$ SD) plasma half-life was observed to be 3.1 ($\pm$ 0.5) hours.

Metabolism

Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation, with naloxone-3-glucuronide 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 25 hours, and 60-70% in 72 hours.

13.8.2. Toxicokinetics

No new toxicokinetics studies with INN were submitted nor required for this application.

13.9. General Toxicology

No new general toxicology studies with NNS were submitted nor were they required for this application.

The Applicant is relying upon FDA's finding of safety for NDA 016636, injectable naloxone (Narcan). This is the same approach employed by the Applicant for the approval of prescription NNS (NDA 208411). At the time of review for NDA 208411, the review division determined that nonclinical studies would not be required considering the clinical trial experience with INN, the acute use of the drug product, and the potentially life-saving indication (DARRTS Reference ID: 3841831).

Since the approval of prescription Narcan (naloxone HCl) nasal spray, an abundance of clinical safety information is available to support the local safety of the drug product. Refer to the clinical review for further information regarding safety of NNS.

13.10. Genetic Toxicology

No new genetic toxicology studies with INN were submitted nor required for this application.

An excerpt from the Rx label for NNS regarding genetic toxicity is provided below:

Naloxone was weakly positive in the Ames mutagenicity test 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.

13.11. Carcinogenicity

No new carcinogenicity studies with INN were submitted. Considering that NNS is an acute use product, these data were not recommended or required for this application.

An excerpt from the Rx label for NNS regarding carcinogenicity is provided below:

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

13.12. Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies with INN were submitted nor required for this application.

An excerpt from the label for NNS regarding reproductive and developmental toxicology studies is provided below:

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 NNS's) based on body surface area comparison). There was no adverse effect on fertility.

Data from fertility and embryonic development, embryo-fetal development, and pre- and postnatal developmental reproduction studies in rats and an embryo-fetal study in mice were previously submitted to support NDA 016636 Narcan (naloxone HCl) injection, which was previously reviewed (see nonclinical review by Dr. Edward Tocus, dated May 12, 1969) and are adapted into the pharmacology/toxicology review for prescription NNS (NDA 208411).

For a summary of the reproductive and developmental toxicology studies originally conducted under NDA 016636, refer to the pharmacology toxicology (P/T) review conducted for prescription NNS (DARRTS Reference ID: 3841831).

13.13. Integrated Summary and Safety Evaluation

The Applicant, Emergent Operations Ireland Limited (Emergent LTD), submitted supplement-006 for the full prescription-to-nonprescription switch of Narcan (naloxone hydrochloride) nasal spray, 4 mg configuration. The drug product is indicated for the treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. The intended patient population is adults and children, including neonates.

No new pharmacology or toxicology information was submitted to this supplement, nor was it required.

The proposed nonprescription intranasal formulation, dose, duration of use, and route of administration are the same as the approved prescription Narcan (naloxone HCl) nasal spray.

Drug Product Device

As described under Regulatory History, PMR 3707-1 was issued on September 23, 2019, at the time of approval of CMC supplement -002 to address the potential for volatile compounds to leach from the secondary CCS and enter the drug product solution (DARRTS Reference ID: 4495636). The Applicant submitted the requested extractable assessment. Note, at the time of filing supplement-006, the P/T group of the prescription product was still reviewing the extractable assessment submitted to fulfill the PMR. Specifically, in October 2022, the P/T team from Office of Neuroscience-Division of Pharmacology Toxicology Neurology reached out to the P/T team in Nonprescription Drug Pharmacology Toxicology Staff (NPD-PTS) regarding the outstanding PMR. This was noted in the NPD-PTS filing review of supplement-006 (DARRTS Reference ID: 5083326).

The Narcan (naloxone HCl) nasal spray drug product is an aqueous solution presented in borosilicate glass vial closed with a chlorobutyl rubber plunger which in turn is mounted into a unit-dose nasal spray device. The device is a nonpressurized dispenser delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 100 µL ([Figure 10](#)). See eCTD Section 2.3.P.1, Description and Composition of the Drug Product.

Figure 10. Diagram of the Narcan (Naloxone HCl) Nasal Spray With Device Components (Not to Scale)



Source: eCTD sequence number 422, 3.2.P Unit Dose Nasal Device Description and Composition of the Drug Product

In an internal meeting on February 8, 2023, the Office of Neuroscience-Division of Pharmacology Toxicology Neurology P/T team conveyed to the review team of NDA 208411 that the extractable information submitted for the outstanding PMR (issued with the approval of supplement-002) was considered adequate from the nonclinical perspective. Regarding the container closure system under supplement-006, CMC reviewer Dr. Sarah Zimmerman stated that (b) (4) was being used in part of the CCS, and that an extraction study had been submitted under an annual report, with no substances identified above the analytical evaluation threshold for NPD-PTS to review. Refer to the CMC review in Panorama under supplement-006 for additional information.

From the nonclinical perspective, supplement-006 is approvable.

14. Clinical Pharmacology

No new clinical pharmacology studies were submitted for this supplement. See Section [6.3.1](#) for a high-level summary of relevant clinical pharmacology information from the original NDA review.

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Not applicable.

14.3. Bioanalytical Method Validation and Performance

Not applicable.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

Not applicable.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

Not applicable.

16. Efficacy

Not applicable.

17. Clinical Safety

17.1. Review of the Applicant's Assessment of FAERS

In the current sNDA, the Applicant has collected postmarketing safety data relating to naloxone products in FDA's Adverse Events Reporting System (FAERS). This analysis covered the period from January 1, 2016, through June 30, 2021. The medical dictionary used for this search was Medical Dictionary for Regulatory Activities (MedDRA) version 24.0.

17.1.1. Limitations

In addition to the usual limitations of postmarketing safety databases, per the Applicant, there were several additional limitations of the FAERS database. The Applicant noted that AE data are not available based on naloxone's dose, duration of use (additional doses used), or marketing

status (prescription or nonprescription) in FAERS. Additionally, case narratives within FAERS were not available to the Applicant for further assessment and confirmation.

17.1.2. General Findings

The Applicant identified 1,134 unique case reports from FAERS during the covering period, which reported a total of 4,139 AEs for all cases. When gender and age information were known, the cases tended to occur somewhat more frequently in females (43.5% versus 40.6% in males) and more frequently in the adult population 18 years of age and older (36.3% compared with 2.5% in pediatric age groups less than 18 years or 7% in geriatric age groups greater than 65 years). Notably, age was unknown in 31.4% of cases.

Route of administration information was available for 496 cases (43.7% of all cases) with similar numbers reporting an intranasal route of administration (264 cases) compared with all other non-nasal routes (232 cases). Route of administration was reported as unknown in 56.3% of cases.

Out of all 1,134 case reports, 741 (741/1,134; 65.3%) were considered serious, including 127 (127/1,134; 11.2%) with fatal outcomes. Serious cases reported a total of 3,491 AEs. Overall, serious outcomes occurred in 343 (343/493; 69.6%) cases involving females and in 269 (269/460; 58.5%) cases involving males. There was a total of two serious cases involving children less than 2 years of age and 24 cases in children ages 2 to less than 18 years. Frequencies of serious outcomes were comparable between general adults 18 to 64 years of age (287/412; 69.7%) and older adults over age 65 years (53/79; 67.1%).

When evaluated by route of administration and seriousness, it was noted that serious outcomes occurred in 26.9% (71/264) of cases involving an intranasal route of administration generating a total of 321 AEs. In contrast, serious outcomes involving a non-nasal route of administration occurred in 88.4% (205/232) of cases and generated 1,029 AEs. Where route of administration information was unknown, serious outcomes were noted in 72.9% (465/638) of those cases, which generated the majority of AEs (2,141).

Table 17. Baseline Patient Characteristics and Route of Administration by Serious and Nonserious Outcomes

Patient Demographics	Intranasal ^a		Non-nasal ^b		Unknown ^c		Total N=1134
	Serious N=71	Nonserious N=193	Serious N=205	Nonserious N=27	Serious N=465	Nonserious N=173	
Gender							
Female	27	79	75	10	241	61	493 (43.5)
Male	37	100	73	12	159	79	460 (40.6)
Unknown gender	7	14	57	5	65	33	181 (16.0)
Age							
< 2 years	0	0	1	0	1	0	2 (0.2)
2 to < 18 years	0	1	11	0	13	1	26 (2.3)
18 to < 65 years	38	55	78	15	171	55	412 (36.3)
65 years and older	6	10	21	1	26	15	79 (7.0)
Unknown age	27	127	94	11	254	102	615 (54.2)

^a Refers to route of administration category = nasal, intranasal, intranasal, respiratory (inhalation)^b Refers to route of administration category: Oral, Intramuscular, Topical, Sublingual, Transdermal, Subcutaneous, Intravenous (not otherwise specified), Buccal, Intravenous bolus, Retrobulbar^c Refers to route of administration category: Unknown, Other, Blank

Source: Module 5.3.5.3 FAERS Route of Administration Analysis, submitted November 22, 2022, Table 1, page 2

17.1.3. Serious Outcomes by Intranasal Route of Administration

Table 18 provides preferred terms (PTs) that were reported at a frequency of >1% among cases with serious outcomes by intranasal route of administration. The corresponding frequencies of those PTs reported with non-nasal and unknown routes of administration are provided for comparison.

Table 18. Most Frequently Reported Preferred Terms (>1%) for All Serious Cases Associated with Intranasal Route of Administration

Preferred Term	Intranasal		Non-Nasal		Unknown		Total	
	321		1,029		2,141		3,491	
	N	%	N	%	N	%	N	%
Overdose	11	3.4	27	2.6	77	3.6	115	3.3
Vomiting	9	2.8	10	1.0	17	0.8	36	1.0
Death	9	2.8	7	0.7	26	1.2	42	1.2
Drug dependence	9	2.8	23	2.2	80	3.7	112	3.2
Drug ineffective	8	2.5	16	1.6	63	2.9	87	2.5
Loss of consciousness	8	2.5	3	0.3	9	0.4	20	0.6
Drug withdrawal syndrome	7	2.2	9	0.9	31	1.4	47	1.3
Fall	7	2.2	3	0.3	8	0.4	18	0.5
Seizure	7	2.2	3	0.3	17	0.8	27	0.8
Drug abuse	6	1.9	8	0.8	35	1.6	49	1.4
Unresponsive to stimuli	5	1.6	7	0.7	21	1.0	33	0.9
Pneumonia aspiration	5	1.6	1	0.1	6	0.3	12	0.3
Respiratory failure	5	1.6	8	0.8	13	0.6	26	0.7

Preferred Term	Intranasal		Non-Nasal		Unknown		Total	
	321		1,029		2,141		3,491	
	N	%	N	%	N	%	N	%
Diarrhea	4	1.2	7	0.7	9	0.4	20	0.6
Feeling abnormal	4	1.2	1	0.1	2	0.1	7	0.2
Unintentional use for unapproved indication	4	1.2	0	0.0	0	0.0	4	0.1
Agitation	4	1.2	2	0.2	8	0.4	14	0.4

Source: Adapted from Module 5.3.5.3 FAERS Route of Administration Analysis, submitted November 22, 2022, Appendix I, page 8

Overall, it is noted that the frequencies of PTs are relatively comparable between intranasal or non-nasal routes of administration with the largest difference for any single PT being loss of consciousness at 2.2%. These findings are generally reassuring that compared to serious cases involving non-nasal naloxone (which includes long-standing standard of care parenteral dosage forms), cases associated with INN do not appear to show any noteworthy or concerning differences.

17.1.4. Serious Outcomes by Age and Intranasal Route of Administration

With respect to age, it is notable that none of the 71 serious cases involving INN occurred in children (less than 18 years). All serious cases involving INN occurred in adults with a majority occurring in those 18 to less than 65 years (38 cases, 53.5%; generating 215 AEs). There were only 6 cases (8.5%) occurring in the elderly (greater than 65 years), which generated a total of 24 AEs. The remaining 27 cases (38%) were those in which age information was not available; these cases generated a total of 82 AEs.

[Table 19](#) shows PTs from serious cases involving naloxone by the intranasal route that occurred most frequently (at least 1% greater difference) in the elderly as compared to general adults. The greatest differences in frequency occurred in the PT drug abuse (6.5% higher in the elderly). Nine terms held the second greatest difference of 4.2%, including concerning AEs such as cardiac failure, drug withdrawal convulsions, and circulatory collapse. However, it is noted that given the very small number of serious cases and PTs reported among the elderly, it is unclear what significance these differences hold. It is unclear that any conclusion about the relative susceptibility of the elderly to experience serious adverse events compared with general adults can be drawn from these findings. However, it is generally reassuring that there are relatively few serious events involving INN and the elderly.

Table 19. Preferred Terms Reported with >1% Difference in the Elderly Versus General Adults in Serious Cases Involving Intranasal Naloxone

Preferred Term	18 to <65 years N=215		65 years and older N=24		% Difference
	n	%	n	%	
Drug abuse	4.0	1.9	2.0	8.3	6.5
Cardiac failure	0.0	0.0	1.0	4.2	4.2
Drug withdrawal convulsions	0.0	0.0	1.0	4.2	4.2
Encephalopathy	0.0	0.0	1.0	4.2	4.2
Headache	0.0	0.0	1.0	4.2	4.2
Restlessness	0.0	0.0	1.0	4.2	4.2
Hyperhidrosis	0.0	0.0	1.0	4.2	4.2
Hospitalization	0.0	0.0	1.0	4.2	4.2
Self-medication	0.0	0.0	1.0	4.2	4.2
Circulatory collapse	0.0	0.0	1.0	4.2	4.2
Cardiac arrest	1.0	0.5	1.0	4.2	3.7
Death	1.0	0.5	1.0	4.2	3.7
Pain	1.0	0.5	1.0	4.2	3.7
Intentional product misuse	1.0	0.5	1.0	4.2	3.7
Respiratory arrest	1.0	0.5	1.0	4.2	3.7
Sneezing	1.0	0.5	1.0	4.2	3.7
Diarrhea	2.0	0.9	1.0	4.2	3.2
Unintentional use for unapproved indication	2.0	0.9	1.0	4.2	3.2
Hypertension	2.0	0.9	1.0	4.2	3.2
Fall	3.0	1.4	1.0	4.2	2.8
Drug dependence	4.0	1.9	1.0	4.2	2.3
Drug withdrawal syndrome	6.0	2.8	1.0	4.2	1.4

Source: Adapted from Module 5.3.5.3 FAERS Route of Administration Analysis, submitted November 22, 2022, Appendix II, page 31

17.1.5. Deaths

In its evaluation of cases resulting in a fatal outcome, the Applicant notes that a total of 127 deaths were reported (127/1,134; 11.2%). When evaluated by route of administration, the Applicant noted 17 cases involved intranasal and non-nasal routes each, while the rest involved an unknown route of administration. Thus, when route of administration information was known, the frequency of death appeared to be comparable between cases involving intranasal (17/264; 6.4%) and non-nasal (17/232; 7.3%) routes. Besides the PT “death,” the Applicant notes that the most frequently reported PTs from these fatal cases were overdose (28%), toxicity to various agents (24%), drug dependence (17%), drug ineffective (17%), cardiac arrest (17%), drug abuse (11%), pain (6%), and respiratory failure (6%).

Table 20. Fatal Outcomes by Route of Administration

	Intranasal N=264	Non-nasal N=232	Unknown N=638	Total N=1,134
Fatal outcome	17 (17/264; 6.4%)	17 (17/232; 7.3%)	96 (96/638; 15.0%)	130*

Source: Adapted from Module 1.11.3 Clinical Information Amendment, submitted November 22, 2022, Table 1, page 5

* Note: Although 127 cases reported a fatal outcome, three cases reported more than one route of administration. In these instances, each route was accounted (i.e., one case of administration via intramuscular and unknown routes and two cases of administration via intravenous and unknown routes). Therefore, a total of 130 cases is referenced.

17.1.6. Safety Topics of Interest

17.1.6.1. Use Error

The Applicant evaluated FAERS for cases involving naloxone that reported a serious outcome related to use error. The Applicant conducted a search for cases reporting a PT within the MedDRA High Level Group Term “medication errors and other product use errors and issues.” Overall, a total of 91 serious cases (91/1,134; 7.9%) were identified from all routes of administration with the majority of cases having an unknown route (57 cases), 14 cases having an intranasal route, and 21 cases having a non-nasal route. Among cases where route of administration information was known, the frequency of use error appeared to be slightly lower for cases involving intranasal (14/264; 5.3%) compared with non-nasal (21/232; 9.1%) routes.

The use error PTs that demonstrated the greatest differences when comparing intranasal routes of administration with non-nasal routes included “unintentional use for unapproved indication” (4 cases for intranasal and 0 cases for non-nasal) and “wrong technique in product usage process” (2 cases for intranasal and 0 cases for non-nasal). Because case narratives are not available via FAERS, these cases cannot be confirmed. However, considering the relatively small numbers of cases accrued and small numerical differences noted between intranasal and non-nasal routes of administration, these findings are generally reassuring that use error appears to occur infrequently and is overall lower for INN products.

17.1.6.2. Product Ineffective

The Applicant evaluated FAERS for cases involving naloxone that reported a serious outcome related to product ineffectiveness. The Applicant identified a total of 90 serious cases (90/1,134; 7.9%) from all routes of administration that reported the PT “drug ineffective.” The majority of these cases reported an unknown route of administration (70 cases), 8 cases reported an intranasal route, and 16 cases reported a non-nasal route. Among cases where route of administration information was known, the frequency of product ineffectiveness appeared to be slightly lower for cases involving intranasal (8/264; 3%) compared with non-nasal (16/232; 6.9%) routes.

Among these 90 cases, 23 cases were associated with a fatal outcome. The Applicant noted that while case narratives were not available, a qualitative evaluation of the associated PTs and concomitant medications revealed that each of the fatal cases were associated with a combination of multiple substances including fentanyl, alcohol, or other illicit substances as well as multiple AEs, which may confound the outcome. These findings are consistent with the information from ARGUS.

It is acknowledged that there are several reasons in which naloxone may not be effective, including use of naloxone in clinical scenarios where overdose is due to a nonopioid or due to multiple agents. Naloxone may also be less effective in scenarios where overdose is due to superpotent opioids or due to partial opioid agonists. Naloxone is also only effective if it is administered in a timely fashion after overdose occurs.

Considering the relatively small numbers of cases accrued and small numerical differences noted between intranasal and non-nasal routes of administration, these findings are generally reassuring

that product ineffectiveness appears to occur infrequently and is somewhat lower for INN products.

17.1.6.3. Drug Allergy and Hypersensitivity

The Applicant evaluated FAERS for cases involving naloxone that reported a serious outcome related to drug allergy and hypersensitivity. The Applicant identified a total of 16 cases (16/1,134; 1.4%) from all routes of administration that reported a preferred term within the High-Level Group Term “allergic conditions.” The majority of these cases reported an unknown route (14 cases), and the remaining cases reported a non-nasal route. No cases report an intranasal route.

Drug allergy is a known potential AE that can arise from use of naloxone. It is generally reassuring that very few cases were reported in FAERS, and the data are consistent with information from ARGUS.

17.1.6.4. Opioid Withdrawal

The Applicant evaluated FAERS for cases involving naloxone that reported a serious outcome related to opioid withdrawal. The Applicant created a custom query, which included use of the standardized MedDRA query “drug withdrawal” as well as a variety of signs and symptoms more specifically associated with opioid withdrawal.

The Applicant identified a total of 368 potential opioid withdrawal cases from all routes of administration of which 214 (214/1,134; 18.9%) were considered serious. When route of administration was known, 30 serious cases were associated with an intranasal route, 72 serious cases were associated with a non-nasal route, and the remaining 112 serious cases were associated with an unknown route.

Table 21. Potential Opioid Withdrawal Cases by Route of Administration in FAERS

Intranasal N=126 n (%)		Non-Nasal N=85 n (%)		Unknown N=157 n (%)		Total N=368 n (%)
Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	Serious n (%)	Non-Serious n (%)	
30 (23.8)	96 (76.2)	72 (84.7)	13 (15.3)	112 (71.3)	45 (28.7)	368 (100)

Source: Module 5.3.5.3 Supplemental ISS- Acute Opioid Withdrawal Analysis, submitted November 4, 2022, Table 1, page 4

To focus on life threatening manifestations of opiate withdrawal, the Applicant reviewed the reported PTs from all serious cases with attention to specific PTs of interest from the Respiratory (e.g., acute respiratory distress syndrome), Cardiac (e.g., cardiac arrest), and Nervous System Disorders (e.g., seizure) system organ classes (SOCs) that are considered potentially life threatening.

Of the cases reporting a fatal outcome, a total of 65 PTs of interest were collected. The majority (51 events) were collected from cases with an unknown route of administration. PTs of interest were most frequently noted under the Nervous System Disorders SOC (25 events with seizure

events accounting for 6 events) followed by the Respiratory SOC (17 events with respiratory failure accounting for 3 events), and the Cardiac Disorders SOC (14 events with cardiac arrest accounting for 4 events). The numbers of events reported for intranasal and non-nasal routes were similarly low with no particular trend. When the PTs of interest associated with fatal intranasal use were evaluated by age group, it was noted that all events associated with fatal opioid withdrawal occurred in the 18 to less than 65-year age group.

Of the nonfatal cases, a total of 43 PTs of interest were collected. The majority (23 events) were collected from cases with an unknown route of administration. PTs of interest were most frequently noted under the Respiratory SOC (19 events with aspiration pneumonia accounting for 4 events) followed by the Nervous System Disorders SOC (12 events with unresponsive to stimuli accounting for 3 events) and the Cardiac Disorders SOC (11 events with tachycardia accounting for 3 events). The numbers of events reported for intranasal and non-nasal routes were similarly low with no particular trend. When the PTs of interest associated with nonfatal intranasal cases were evaluated by age group, it was noted that all events occurred in the 18 to less than 65-year age group.

No safety trends are noted based on evaluation by route of administration for this safety topic.

17.2. Review of the Applicant's Assessment WHO Vigibase

The World Health Organization (WHO) Vigibase is the adverse drug report database maintained by the Uppsala Monitoring Centre in Sweden. Vigibase collects summaries of clinical reports about individual suspected adverse reaction to pharmaceutical products from national centers in countries participating in the WHO safety program. Case narratives are not available from Vigibase due to international confidentiality restrictions.

Per the Applicant, route of administration information is available through the Vigibase dataset. The Applicant's search of Vigibase was restricted to include only those cases reporting a "nasal", "other", or "unknown" route of administration. The search was designed to omit cases reporting "intravenous" and "intramuscular" to eliminate other product use. "Transmammary" and "transplacental" routes of administration were included due to potential fetal exposure from maternal use.

The medical dictionary used for this search was MedDRA version 23.1.

17.2.1. General Findings

The Applicant identified 1,292 case reports from Vigibase over the period from January 1, 2016, through May 5, 2021, in which naloxone was identified as a suspect drug. A total of 3,276 AEs were collected from all cases. When gender and age information were known, cases tended to occur more frequently in males (53.8% versus 39.8% in females) and more frequently in the adult population 18 years of age and older (72.1% versus 2.5% in pediatric age groups). Age was unknown in 25.5% of cases.

Route of administration information was only available for 246 cases (19% of all cases). 226 (226/1,292; 17.5%) of these cases reported an intranasal route and 20 cases (20/1,292; 1.6%)

reported “other” route, while the majority of the cases reported naloxone use by an unknown route (1,047/1,292; 81%).

17.2.2. Serious Outcomes

Out of all 1,292 case reports, 522 (40.4%) were considered serious, including 131 cases (131/1,292; 10.1%) reporting a fatal outcome. Serious cases reported a total of 1,954 AEs. On face, the overall frequency of serious outcomes appears to be lower in Vigibase than among FAERS data (serious outcomes occurred in 65.3% cases reported in FAERS). However, considering the differences in search methods (i.e., the exclusion of injectable forms of naloxone), it is not unexpected that the frequency of serious outcomes was substantially different and not comparable.

The most frequently reported PTs associated with serious cases in Vigibase are similar to those noted in FAERS. The types of reported PTs were generally expected given the known AE profile of naloxone as well as the underlying condition for which it treats. These findings are generally aligned with the findings noted from ARGUS and FAERS.

Table 22. Most Frequently Reported Preferred Terms (>1%) From All Serious Cases

Preferred Term	n	%
Drug Dependence	63	3.2
Overdose	60	3.1
Drug Ineffective	59	3.0
Dyspnea	44	2.3
Chills	42	2.1
Chest Pain	35	1.8
Toxicity to Various Agents	31	1.6
Vomiting	30	1.5
Drug Withdrawal Syndrome	27	1.4
Death	26	1.3
Pain	25	1.3
Seizure	25	1.3
Cardiac Arrest	22	1.1
Fetal Exposure During Pregnancy	22	1.1
Unresponsive to Stimuli	22	1.1
Nausea	21	1.1
Hyperhidrosis	21	1.1
Blood Pressure Increased	20	1.0
Drug Abuse	20	1.0
Palpitations	19	1.0
Pyrexia	19	1.0

Source: Adapted from Module 5.3.5.3 Integrated Summary of Safety, Appendix I, Table 8, page 311

17.2.3. Safety Topics of Interest

17.2.3.1. Use Error

The Applicant evaluated Vigibase for cases involving naloxone that reported a serious outcome related to use error. Utilizing the same search method previously described, the Applicant identified 46 serious cases (46/1,292; 3.4%) from all routes of administration. Among these

cases, the majority reported an unknown route (21 cases); 9 cases reported an intranasal route, and 17 cases reported a non-nasal route.

The only use error PT that demonstrated a greater number for the intranasal route of administration compared with non-nasal route was “unintentional use for unapproved indication” (3 cases for intranasal and 0 cases for non-nasal).

As case narratives are not available from Vigibase, independent medical assessment of the cases was not possible. Nevertheless, the low numbers of cases identified (particularly for cases involving intranasal route of administration) is consistent with findings from ARGUS and FAERS and does not suggest that use error is a major safety signal.

17.2.3.2. Product Ineffective

The Applicant evaluated Vigibase for cases involving naloxone that reported a serious outcome related to product ineffectiveness. The Applicant identified a total of 68 cases (68/1,292; 5.3%) from all routes of administration that reported the PT “drug ineffective.” The number of cases associated with intranasal route (5 cases) is similar to that associated with non-nasal route (8 cases).

As case narratives are not available from Vigibase, independent medical assessment of the cases was not possible. As discussed previously, there are a number of reasons in which naloxone may not be effective. There does not appear to be a significant difference based on route of administration. The findings noted in Vigibase are generally consistent with findings from ARGUS and FAERS.

17.2.3.3. Drug Allergy and Hypersensitivity

The Applicant evaluated Vigibase for cases involving naloxone that reported a serious outcome related to drug allergy and hypersensitivity. The Applicant identified a total of 23 cases (23/1,292; 1.8%) from all routes of administration that reported a PT within the High-Level Group Term “allergic conditions.” The majority of cases reported an unknown route of administration (20 cases). No cases were reported with an intranasal route and 3 cases were reported with non-nasal route.

Drug allergy is a known potential AE that can arise from use of naloxone. It is generally reassuring that very few cases were reported overall in Vigibase; thus, supporting findings from the ARGUS and FAERS databases.

17.2.3.4. Naloxone-Induced Precipitated Withdrawal

The Applicant evaluated Vigibase for cases involving naloxone that reported a serious outcome related to naloxone-induced precipitated withdrawal. Utilizing the same search method previously described, the Applicant identified a total of 627 cases of potential opioid withdrawal from all routes of administration. 233 (233/627; 37%) were considered serious and accounted for 352 AEs. When route of administration was known, 24 serious cases were associated with an intranasal route, 41 serious cases were associated with a non-nasal route, and the remaining 168 cases were associated with an unknown route.

Similar to its evaluation of FAERS data, in order to focus on life threatening manifestations of opiate withdrawal, the Applicant reviewed the reported PTs from all serious cases with attention to specific PTs from the Respiratory, Cardiac and Nervous System Disorders SOC that are considered potentially life threatening.

Of the cases reporting a fatal outcome, a total of 52 PTs of interest was collected. The majority (45 events) were collected from cases with an unknown route of administration. PTs of interest were most frequently noted under the Nervous System Disorders SOC (21 events with seizure accounting for 6 events) followed by the Respiratory SOC (13 events with dyspnea, pulmonary edema, and respiratory failure each accounting for 2 events) and Cardiac Disorders SOC (8 events with tachycardia accounting for 2 events). The numbers of events reported for intranasal and non-nasal routes were similarly low with no particular trend. When the PTs of interest associated with fatal intranasal use were evaluated by age group, it was noted that all events occurred in the 18 to less than 65-year age group.

Of the nonfatal cases, a total of 29 PTs of interest were collected. 14 events were collected from cases with an unknown route of administration. PTs of interest were most frequently noted under the Respiratory SOC (16 events with aspiration pneumonia accounting for 4 events) followed by the Nervous System Disorders SOC (7 events with unresponsive to stimuli accounting for 3 events) and the Cardiac Disorders SOC (6 events with bradycardia accounting for 2 events). The numbers of events reported for intranasal and non-nasal routes were similarly low with no particular trend. When PTs of interest associated with nonfatal intranasal cases were evaluated by age group, it was noted that all events occurred in the 18 to less than 65-year age group.

These results are consistent with the findings from ARGUS and FAERS.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

According to the prescription label for Narcan (naloxone HCl) nasal spray (NDA 208411) the mechanism of action is described as:

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.

For further information, refer to the nonclinical P/T review of the prescription NNS by Drs. Newton Woo and Richard Mellon dated November 2, 2015 (DARRTS Reference ID: 3841831).

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Not applicable.

23. Labeling: Key Changes and Considerations

23.1. Approved Labeling Types

Upon approval of this [application/efficacy supplement], the following labeling documents will be FDA-approved:

- 2-count outer carton
- Quick start guide
- Immediate container (blister package) label
- Drug-delivery device label

23.2. Approach to the Labeling Review

The interdisciplinary scientist review team in Division of Nonprescription Drugs I assessed the labeling proposed in NDA 208411/S-006 to determine if it:

1. Follows nonprescription labeling regulation⁸
2. Appropriately integrates approved Narcan prescription labeling elements for consumers (i.e., includes information in consumer-friendly terms so that the drug product is safe and effective in the absence of supervision by a health professional)
3. Matches the recommendations and determinations from other review disciplines

Review of this application also includes a comparison to an FDA generated DFL for naloxone nasal spray products. To encourage drug manufacturers to develop a nonprescription naloxone drug product, FDA developed and validated a model DFL. The validation studies of the model label were announced in *Federal Register* (87 FR 68702, November 16, 2022) and published in *The New England Journal of Medicine* ([Cohen et al. 2020](#)).

For this review, the proposed draft labeling for Narcan (naloxone HCl, 4 mg, nasal spray) was preliminarily assessed as to whether the DFL was presented in accordance with relevant

regulation⁸ and FDA guidance and recommendations in above references ([August 2010](#); [Cohen et al. 2020](#)). The draft label also assesses how adequately important information from the prescription labeling was conveyed outside the DFL, such as the quick start guide and principal display panel (PDP) information, to ensure safe and effective use of this product by consumers.

Finally, this labeling review considers whether additional critical labeling statements are necessary, and whether the proposed nonprescription labeling aligns with current labeling requirements for drugs delivered using a nasal spray device, and if it does, is it adequate (see FDA guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation* ([July 2002](#))).

Table 23. Proposed Draft Labeling

Proposed Label	Date Submitted
2-Count Outer Carton (b) (4)	September 29, 2022
2-Count Outer Carton (b) (4)	September 29, 2022
2-Count Outer Carton-Not for Retail Distribution	September 29, 2022
Immediate Container (Blister Package) Label	September 29, 2022
Drug-Delivery Device Label	September 29, 2022

Source: FDA reviewer generated table using labeling materials from NDA 208411/S-006 module 1.14.1.1 submitted September 29, 2022.

23.3. Review Issues

Nonprescription Labeling Regulation

The proposed labeling was reviewed using the CFR, FDA guidance for industry, and official compendia. Regulation relevant to the identified review issues includes 21 CFR 201.60, 21 CFR 201.61, 21 CFR 201.62, 21 CFR 201.66, 21 CFR 299.4, guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation* ([July 2002](#)), guidance for industry *Labeling OTC Human Drug Products — Questions and Answers* ([December 2008](#)), and Over-The-Counter Human Drugs Labeling Requirements (64 FR 13254 at 13268, March 17, 1999).

Consumer Friendly Labeling

The proposed labeling is largely based on FDA’s model naloxone DFL, except for information specific to the Applicant’s drug-delivery device (i.e., Step 2 of the instructions). The suitability of this element was tested via HFVS (see the review by the Division of Medication Error Prevention and Analysis, (DARRTS Reference ID: 5139093). The labeling outside of the DFL includes the PDP, blister, and immediate container labeling. The interdisciplinary scientist has made several recommendations for improved consumer accessibility and understanding (see Section [23.4.5](#)). These recommendations are based on FDA plain language policy, past FDA

⁸ The regulations for constructing a nonprescription drug label (for reference) are primarily found in the following sections of the Code of Federal Regulations (21 CFR) Part 201: Subpart A—General Labeling Provisions, Subpart C—Labeling Requirements for OTC drugs, which provides the labeling for packaging (PDP at §201.60 and Statement of Identity (SOI) at §201.61, etc.) and content and format of the DFL at §201.66 (c) and (d), Subpart G—Packaging and Labeling Control which provides the labeling for the tamper-evident packages at §211.132.

consumer studies, and the previously mentioned nonprescription labeling FDA guidances for industry ([December 2008](#); [July 2002](#)).

Does the Labeling Include Recommendations from All Review Disciplines?

The interdisciplinary scientist will confirm that labeling follows the review team's recommendations, including indication, warnings, directions, storage conditions, etc., upon completion of each discipline's review and recommendation.

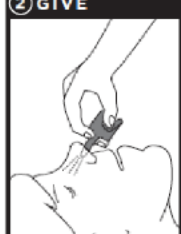
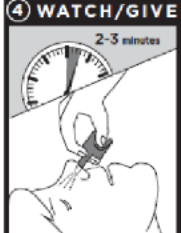
23.4. Assessment

23.4.1. Drug Facts Label

Nonprescription labeling provides critical information in consumer-friendly language so that consumers can use nonprescription drug products safely and effectively. Most of this information is placed in the DFL, a section of nonprescription drug labeling that is presented in a standardized format that lists the active ingredient, purpose, uses, warnings, directions, and inactive ingredients, in accordance with 21 CFR 201.66(c) and (d). In a prescription to nonprescription switch, content from the prescribing information of the Rx product is converted to plain language. Testing (e.g., labeling comprehension and human factors) is then used to show that consumers can use follow the newly created labeling and use the nonprescription drug product safely and effectively.

FDA developed a model DFL to encourage drug manufacturers to develop a nonprescription naloxone drug product (see [Figure 11](#)). It was our expectation that the only change in content between FDA's model DFL for naloxone and the Applicant's DFL will be specific to Applicant's nasal spray drug delivery device. In this case, the changes are limited to step 2 of the "**Directions.**" Content was also added to empty portions of the model DFL, including the "**Other information,**" "**Inactive ingredients,**" and "**Questions?**" sections.

Figure 11. FDA Model Drug Facts Label

Drug Facts	
Active ingredient (in each XX) Purpose Naloxone hydrochloride x mg..... Emergency treatment of opioid overdose	
Uses	
- to "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin - this medicine can save a life	
Directions	
    	Step 1: CHECK if you suspect an overdose CHECK for a <u>suspected overdose</u>: the person will not wake up or is very sleepy or not breathing well - yell "Wake up!" - shake the person gently - if the person is not awake, go to Step 2 Step 2: GIVE 1st dose GIVE the 1st dose of this medicine - insert in NOSE and press Step 3: CALL CALL 911 immediately after giving the 1st dose Step 4: WATCH & GIVE WAIT 2-3 minutes after the 1st dose to give the medicine time to work - if the person <u>wakes up</u>: Go to Step 5 - if the person does <u>not wake up</u>: CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up - it is safe to keep giving doses Step 5: STAY STAY until ambulance arrives: even if the person wakes up GIVE another dose if the person becomes very sleepy again - You may need to give all the doses in the pack

Warnings

When using this product some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.

Other Information

- store at room temperature
- [advise insert tamper evident statement here]

Inactive ingredients**Questions?**

(phone number, website)

The only substantive change to the “**Directions**” in FDA’s model DFL label is the Applicant’s use of instructions for use associated with a nasal spray drug delivery device ([Figure 12](#)). This change was accompanied with a pictogram (outside of the DFL) showing a hand holding a device that looks like the NNS device into the nostril of an apparently unconscious person. This labeling content was tested in a HFVS, which was the subject for discussion at the advisory committee meeting.

Applicant also added information listed below:

1. A “Keep out of reach of children” warning to the “*Warnings*” section,
2. Storage conditions to the “*Other information*” section,
3. A tamper evident statement to “*Other information*” section,
4. The product’s inactive ingredients to the “*Inactive ingredients*” section,
5. A telephone of source that will answer questions or record complaints to the “*Questions?*” section.

The labeling contains a single warning that adequately warns consumers about AEs most likely to occur with the product, such as the expected behaviors of the overdose victim when they regain consciousness.

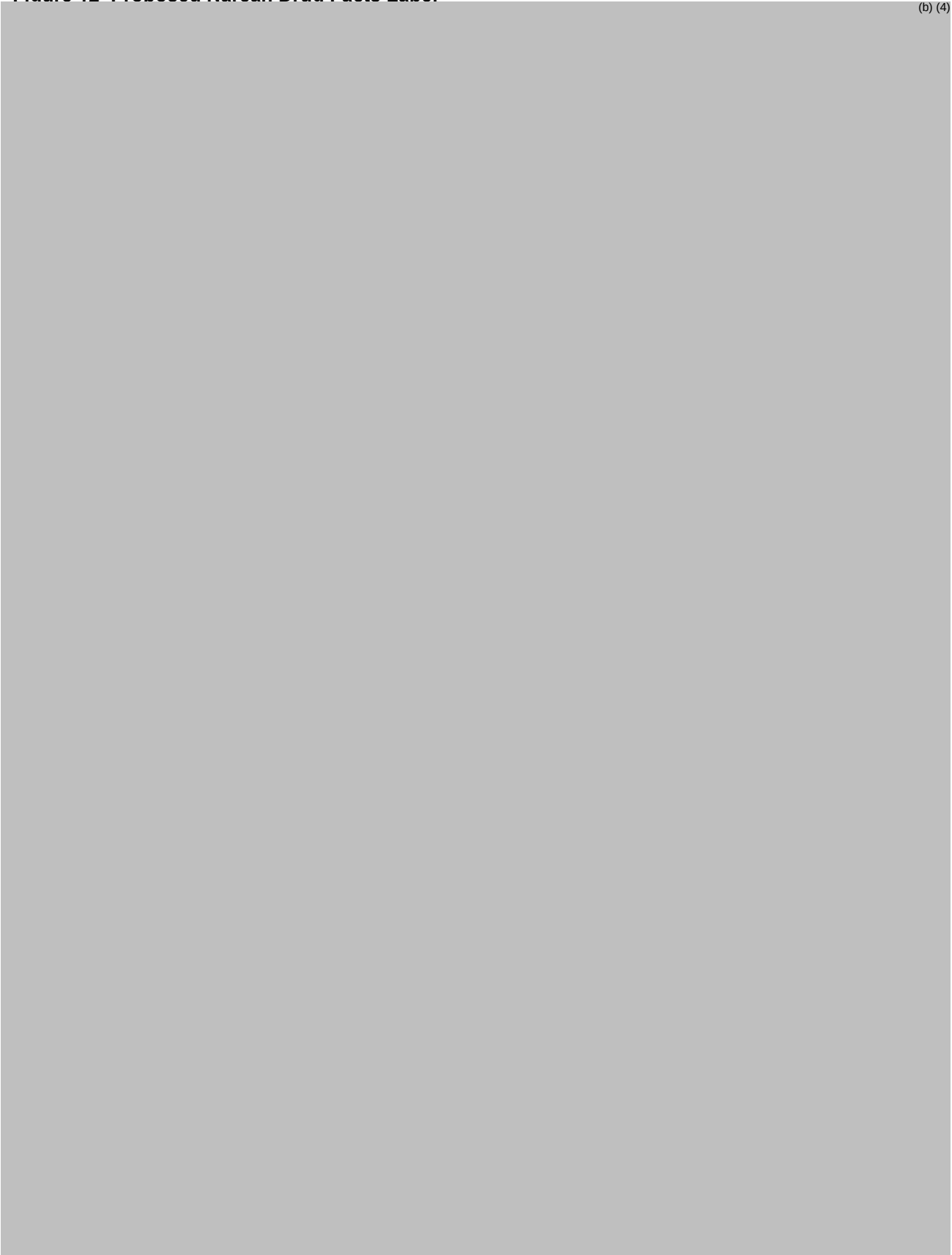
As part of the final review, the labeling review team will consider whether the Applicant has used the appropriate formatting for the DFL. DFL annotation (e.g., print and line specifications) was not provided in the original submission.

NDA 208411/S-006

Narcan (naloxone hydrochloride) nasal spray, 4 mg

Figure 12 Proposed Narcan Drug Facts Label

(b) (4)





23.4.2. Principal Display Panel

The PDP is the most prominently displayed panel and is the most likely to be examined by consumers before purchase. It informs the consumer of the identity of contents (i.e., statement of identity) and how much drug product is contained in the packaging (i.e., declaration of net quantity of contents statement). It is important that this information is displayed prominently and is not obstructed by clutter. Nonprescription labeling has adopted standardized formatting and language for the statement of identity and net quantity to assist consumers during drug selection.

The review team notes that changes were made to the PDP between when the Human Factors testing was completed and submission of the to-be-marketed label ([Figure 13](#)). This discrepancy is noted in review information provided by the Division of Medication Error Prevention and Analysis (DARRTS Reference ID: 5139093) and was a topic for discussion at the Advisory Committee meeting and review issues noted will be resolved during labeling negotiations, discussed later in this review.

The review team has also identified proposed labeling statements that must be changed to comply with regulation for consumer-friendly language and standardized formatting. For instance, the proposed statement of identity “(naloxone HCl) nasal spray 4 mg OPIOID OVERDOSE RESCUE” is incorrect in both its content and how it is displayed. In addition, the proposed declaration of net quantity of contents statement also incorrectly identifies the dosage form as “Single-Dose Devices.”

Figure 13 Proposed PDP



Source: "Narcan Nasal Spray 4 mg OTC Carton-New," module 1.14.1.1 NDA 208411/S-006 dated Sept 29, 2022
Abbreviations: PDP, principal display panel; HCl, hydrochloride

23.4.3. Blister Pack Labeling

In addition to the outer carton (containing the PDP and DFL), the Applicant provided labels for a blister package ([Figure 14](#)) and for the drug delivery device ([Figure 15](#)). It appears that the Applicant followed FDA's guidance for prescription nasal spray devices when generating the blister label (see FDA guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation* ([July 2002](#))). However, the proposed blister label is not consumer friendly because the information is cluttered and disorganized. It will need revision to convey important information clearly that includes content, storage conditions, and a warning to avoid testing the nasal spray before use. The blister labeling also provides an opportunity to address common user mistakes that were observed in the human factors study. For instance, the prominence of the statement, "For use in the nose only" can be increased to inform consumers where to use the nasal spray. These issues will be resolved during labeling negotiations, discussed later in this review.

NDA 208411/S-006

Narcan (naloxone hydrochloride) nasal spray, 4 mg

Figure 14. Proposed Blister Pack Label

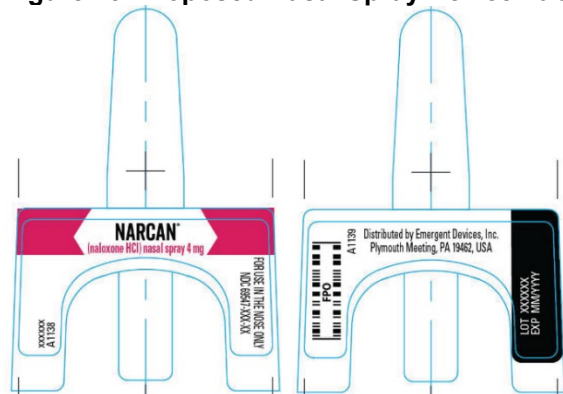


Source: Blister Label," module 1.14.1.1 NDA 208411/S-006 dated Sept 29, 2022

23.4.4. Nasal Spray Device Labeling

The label placed directly on the nasal spray drug delivery device appears appropriate, following a format adjustment to the statement of identity for the drug. This issue will be resolved during labeling negotiations, discussed later in this review.

Figure 15. Proposed Nasal Spray Device Labeling



Source: OTC Device Label," module 1.14.1.1 NDA 208411/S-006 dated Sept 29, 2022

23.4.5. Outstanding Items to Address During Label Negotiations

There are outstanding issues regarding the proposed nonprescription labels that still need to be addressed with the Applicant to determine whether all proposed labeling meets all applicable labeling regulations. As such, the labels will be modified prior to approval of this naloxone nasal spray product. The labeling team will negotiate these changes with the Applicant prior to FDA action and provide an approval recommendation in a subsequent review. This review will be

uploaded to DARRTS separately as a primary labeling review no later than the product approval date. Recommended changes to the label will be informed by the discussion and recommendations provided by members of the Advisory Committee panel. However, FDA has noted the following items to be addressed:

1. FDA will request clean labeling with annotation that demonstrates the DFL formatting meets the requirements found in 21 CFR 201.66. A simple legend is sufficient.

PDP

1. The proposed statement of identity “(naloxone HCl) nasal spray 4 mg OPIOID OVERDOSE RESCUE” is incorrect in both its content and how it is displayed. It must include the established name, “naloxone HCl 4 mg nasal spray,” that is immediately followed by the general pharmacological category, “Emergency Treatment of Opioid Overdose,” which matches the purpose found in the DFL. This format should be used wherever the labeling includes the established name of the drug.
2. Data to support the promotional statements, (b) (4) and (b) (4) located on the PDP, were not provided.
3. The net quantity displayed on the PDP must include the dosage form “nasal sprays.” Unlike other nonprescription nasal spray devices, the naloxone nasal spray devices contain only a single dose. Per 21 CFR 201.62(a), the net quantity statement needs to be augmented to inform that each nasal spray contains only 1 dose.
4. The net content (fill) volume located on the PDP must presented in fluid ounces (i.e., fl oz.) first, followed by milliliters (i.e., mL) in parentheses (i.e., “0.003 fl oz (0.1 mL) each”).

DFL

1. The proposed DFL contains the statement “Narcan OTC nasal spray” under Step 2 in the “**Directions**.” The use of proprietary names and promotional statements in the DFL is not permitted, per Over-The-Counter Human Drugs Labeling Requirements, published on March 17, 1999 (64 FR 13254 at 13268). The label should be revised by removing the proprietary name from the DFL.
2. The “**Active ingredient**” heading should read “**Active ingredient** (in each spray)” instead of “**Active ingredient** (in each 0.1 mL).”
3. Children may have to administer this drug product. The warning “**Keep out of reach of children**” should be removed.
4. Revise your labeling, both outer carton and blister, to present the storage conditions in a clear range of temperatures that follows the prescription labeling storage conditions, “● store at 20 to 25°C (68 to 77°F).”
5. Under “**Inactive ingredients**” change “disodium ethylenediaminetetraacetate” to “edetate disodium”.
6. Per 21 CFR 201.66(d)(5), arrows will be needed to signal continuation of the DFL on the other panels of the container.

Blister Label

1. The blister label is cluttered and disorganized. It will need revision to clearly convey important information that includes content, storage conditions, instruction to use in nose only, and a warning to avoid testing the nasal spray before use.
2. Adding a prominent statement to the nasal spray device and the blister label that states that the device contains only one dose will help ensure that consumers are careful to preserve the drug product in the device until needed.

24. Postmarketing Requirements and Commitments

Not applicable.

25. Financial Disclosure

Not applicable.

26. 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):49-58.

Aguirre, BA, C Lim, C Morton, MH Lev, and JA Barash, 2021, Assessing Memory Loss in a Young Adult With Substance Use Disorder: Remember the Timing of Presentation, *Harv Rev Psychiatry*, 29(3):246-250.

Alho, H, N Mäkelä, J Isotalo, L Toivonen, J Ollikainen, and S Castrén, 2022, Intranasal as Needed Naloxone in the Treatment of Gambling Disorder: A Randomised Controlled Trial, *Addictive Behaviors*, 125:107127.

Alsharif, P, T Satty, C Ramdin, A Martinho, M Patel, and LS Nelson, 2021, Administration of Naloxone During COVID-19 by an Urban, Hospital-Based Emergency Medical Service, *SAEM21 Abstracts, Acad Emerg Med*, 28:S112.

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.

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. In: Nelson, LS, MA Howland, NA Lewin, SW Smith, LR Goldfrank and RS Hoffman, editors, *Goldfrank's Toxicologic*

NDA 208411/S-006

Narcan (naloxone hydrochloride) nasal spray, 4 mg

Emergencies, 11e, New York, NY: McGraw-Hill Education, access.mhmedical.com/content.aspx?aid=1163017507.

Dingledine, R, LL Iversen, and E Breuker, 1978, Naloxone as a GABA Antagonist: Evidence From Iontophoretic, Receptor Binding and Convulsant Studies, *Eur J Pharmacol*, 47(1):19-27.

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

Green, TC, P Case, H Fiske, J Baird, S Cabral, D Burstein, V Schwartz, N Potter, AY Walley, and J Bratberg, 2017, Perpetuating Stigma or Reducing Risk? Perspectives From Naloxone Consumers and Pharmacists on Pharmacy-Based Naloxone in 2 States, *J Am Pharm Assoc* (2003), 57(2s):S19-S27.e14.

Haffajee, RL and RG Frank, 2018, Making the Opioid Public Health Emergency Effective, *JAMA Psychiatry*, 75(8):767-768.

Holland-Hall, C and G Burstein, 2016, Adolescent Development. In: Kliegman, R, BF Stanton and JW St. Geme, editors, *Nelson Textbook of Pediatrics*, 20e, Philadelphia, PA: Elsevier, 926-936.

Kahn, LS, M Wozniak, BM Vest, and C Moore, 2022, "Narcan Encounters:" Overdose and Naloxone Rescue Experiences Among People Who Use Opioids, *Subst Abus*, 43(1):113-126.

Kline, A, D Mattern, N Cooperman, P Dooley-Budsock, JM Williams, and S Borys, 2020, "A Blessing and a Curse:" Opioid Users' Perspectives on Naloxone and the Epidemic of Opioid Overdose, *Subst Use Misuse*, 55(8):1280-1287.

Kuehn, BM, 2023, Fentanyl Drives Startling Increases in Adolescent Overdose Deaths, *JAMA*, 329(4):280-281.

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.

Leung, TC, S Colyer, and S Zehireva, 2021, An Outcome Study on the Naloxone Education/Dispensing Program for Departure Patients at Cermak Health Services of Cook County, *J Correct Health Care*, 27(1):11-13.

Lozo, KW, LS Nelson, C Ramdin, and DP Calello, 2019, Naloxone Deserts in NJ Cities: Sociodemographic Factors Which May Impact Retail Pharmacy Naloxone Availability, *J Med Toxicol*, 15(2):108-111.

Meyerson, BE, JD Agle, A Davis, W Jayawardene, A Hoss, DJ Shannon, PT Ryder, K Ritchie, and R Gassman, 2018, Predicting Pharmacy Naloxone Stocking and Dispensing Following a Statewide Standing Order, *Indiana 2016, Drug Alcohol Depend*, 188:187-192.

Murphy, SM, JR Morgan, PJ Jeng, and BR Schackman, 2019, Will Converting Naloxone to Over-the-Counter Status Increase Pharmacy Sales?, *Health Serv Res*, 54(4):764-772.

Pergolizzi, JV, Jr., A Dahan, J Ann LeQuang, and RB Raffa, 2021, Overdoses Due to Fentanyl and Its Analogues (F/FAs) Push Naloxone to the Limit, *J Clin Pharm Ther*, 46(6):1501-1504.

NDA 208411/S-006

Narcan (naloxone hydrochloride) nasal spray, 4 mg

Svensson, AI, A Berntsson, M Eirefelt, and B Söderpalm, 2000, Naloxone Antagonizes GABA(A)/Benzodiazepine Receptor Function in Rat Corticohippocampal Synaptoneurosomes, *J Neural Transm (Vienna)*, 107(3):261-270.

Tataris, KL, JM Weber, L Stein-Spencer, and SE Aks, 2013, The Effect of Prehospital Nebulized Naloxone on Suspected Heroin-Induced Bronchospasm, *Am J Emerg Med*, 31(4):717-718.

Thakur, T, M Frey, and B Chewning, 2020, Pharmacist Roles, Training, and Perceived Barriers in Naloxone Dispensing: A Systematic Review, *J Am Pharm Assoc (2003)*, 60(1):178-194.

Tsai, AC, MV Kiang, ML Barnett, L Beletsky, KM Keyes, EE McGinty, LR Smith, SA Strathdee, SE Wakeman, and AS Venkataramani, 2019, Stigma as a Fundamental Hindrance to the United States Opioid Overdose Crisis Response, *PLOS Medicine*, 16(11):e1002969.

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

Guidances for Industry

Guidance for Industry *Q3B(R2) Impurities in New Drug Products* (August 2006).

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

Guidance for Industry *Labeling OTC Human Drug Products - Questions and Answers* (December 2008).

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

Guidance for Industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation* (July 2002).

Others

Administration for Strategic Preparedness & Response, 2022, Renewal of Determination That a Public Health Emergency Exists Nationwide as a Result of the Continued Consequences of the Opioid Crisis, U.S. Department of Health & Human Services, accessed March 17, 2023, <https://aspr.hhs.gov/legal/PHE/Pages/Opioid-22Dec2022.aspx>.

Ahmad, F, J Cisewski, L Rossen, and P Sutton, 2023, Provisional Drug Overdose Death Counts, National Center for Health Statistics, accessed March 18, 2023, <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>.

Correal, A, 2018, Overdose Antidote is Supposed to be Easy to Get. It's Not., *The New York Times*, <https://www.nytimes.com/2018/04/12/nyregion/overdose-antidote-naloxone-investigation-hard-to-buy.html>.

Emergent Devices Inc., 2020, Prescribing Information: NARCAN - Naloxone Hydrochloride Spray, accessed March 18, 2023, <https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/724df050-5332-4d0a-9a5f-17bf08a547e1/spl-doc?hl=Narcan>.

Food and Drug Administration, 2022, Information About Naloxone, accessed March 25, 2023, <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-about-naloxone>.

Legislative Analysis and Public Policy Association, 2023, Naloxone Access: Summary of State Laws, accessed January 13, 2023, <https://legislativeanalysis.org/naloxone-summary-of-state-laws/>.

Lloyd, J, 2018, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Director Memorandum for the AADPAC/DSaRM Meeting to Discuss Strategies to Increase the Availability of Naloxone Products Intended for Use in the Community, <https://www.fda.gov/media/121182/download>.

National Coordinating Council for Medication Error Reporting and Prevention, 2023, NCC MERP Taxonomy of Medication Errors, accessed March 18, 2023, <https://www.nccmerp.org/taxonomy-medication-errors-now-available>.

Pattani, A, 2021, To Save Lives, Overdose Antidote Should Be Sold Over-the-Counter, Advocates Argue, NPR, <https://www.npr.org/sections/health-shots/2021/12/14/1063865914/to-save-lives-overdose-antidote-should-be-sold-over-the-counter-advocates-argue>.

The White House, 2021, White House Releases State Model Law to Help Make Access to Naloxone Consistent Across the Country, accessed March 19, 2023, <https://www.whitehouse.gov/ondcp/briefing-room/2021/11/17/white-house-releases-state-model-law-to-help-make-access-to-naloxone-consistent-across-the-country/>.

U.S. Department of Health and Human Services, 2018, Strategy to Combat Opioid Abuse, Misuse, and Overdose: A Framework Based on the Five Point Strategy, accessed March 19, 2023, <https://www.hhs.gov/c/abstract/?docid=816001>.

27. Review Team

Table 24. Reviewers of Integrated Assessment (Digital Signatures in Table 26 Listed in Same Order)

Role	Name(s)
Interdisciplinary Scientist	Robert Bahde
Interdisciplinary Scientist TL	Kevin Lorick
Human Factors Reviewer (DMEPA II)	Millie Shah
Human Factors TL (DMEPA II; Acting)	Colleen Little
Associate Director for Human Factors (DMEPA II)	Lolita Sterrett
Deputy Division Director (DMEPA II)	Chi-ming (Alice) Tu
Chemist (CMC)	Sarah Zimmermann
Senior Product Quality Assessor (CMC)	Joyce Crich
Branch Chief (CMC)	Ramesh Raghavachari
Bio Medical Engineer (CDRH)	Kyran Gibson
Assistant Director (CDRH)	Alan Stevens
Nonclinical Reviewer	Chibueze Ihunnah
Nonclinical Secondary Reviewer	Jane Sohn

Role	Name(s)
Associate Director for Therapeutic Review (DAAP)	Celia Winchell
Social Science Reviewer	Paul Jones
Regulatory Project Manager	Phong Pham
CPMS	Dan Brum
Clinical Reviewer	Dorothy Chang
Cross-Disciplinary Team Leader	Jody Green
Division Director (DAAP)	Rigoberto Roca
Division Director (DNPDI)	Nushin Todd
Office Director (ON; Acting)	Teresa Buracchio
Office Director (ONPD)	Theresa Michele

Abbreviations: CDRH, Center for Devices and Radiologic Health; CMC, Chemistry, Manufacturing and Control; DAAP, Division of Anesthesia and Analgesia Products; DMEPA II, Division of Medication Error Prevention and Analysis II; DNPDI, Division of Nonprescription Drugs I; HF, Human Factors; ON, Office of Neuroscience; ONPD, Office of Nonprescription Drugs; TL, Team Leader

Table 25. Additional Reviewers of Application/Advisory Committee (Digital Signatures Not Required)

Office or Discipline	Name(s)
ONPD	Karen Minerve Murry (DOD)
ON	Billy Dunn (OD)
OSE	Abiola Olagundoye (SRPM), Wendy Brown (SRPM TL), Darrell Jenkins (CPMS), Gerald Dal Pan (OD)
Social Science (DNPDI)	Barbara Cohen
Mathematical Statistician	Rongmei Zhang, Yong Ma (Lead)
DAAP	Kimberly Compton (RPM), Matthew Sullivan (CPMS), Zachary Dezman (Rev)
DPMH	Ndidi Nwokorie (Rev), Mona Khurana (TL), CAPT Anissa Davis-Williams (RPM), George Greeley (CPMS)
CDER Combination Products	Kristina Lauritsen
CDRH	Courtney Evans
OPQ	Avani Patel (RPM)
OSE/Drug Use	Jae Wook Yoo (Rev), Corinne Woods (TL)
OSE/DEPI	Tamra Meyer (AD), Amy Seitz (TL), Benjamin Booth (TL), Rajdeep Gill (DDD)
OSE/DPV	Allison Lardieri (Rev), Lynda McCulley (TL), Karen Konkel (Lit Rev), Sarah Kang (Safety Eval), Jamie Klucken (Safety Eval), Ida-Lina Diak (DDD)
OSE/DMEPA II	Grace Jones (Rev), Ashleigh Lowery (TL), Danielle Harris (DD)
OSE/DMAMES	Yelena Maslov (Rev), Zachary Oleszczuk (DDD)
ORP	Ayako Sato, David Joy
OCC	Deborah Chasan-Sloan, Sherene Sepehri, Josh Brown
OND Policy	Jagjit Grewal
OCOMM	Kristen Booze
DACCM	Moon Hee Choi (DFO), Philip Bautista (TL)
Economist	Will Liu, Andreas Schick
IAMA	Nikia Morris, Rhonda Hearn-Stewart
Medical Editors	James Ebersole, Toria Gilbert, Hyo Sook Song

Office or Discipline	Name(s)
Other	

Abbreviations: CDER, Center for Drug Evaluation and Research; DACCM, Division of Advisory Committee and Consultant Management; DD, Division Director; DDD, Deputy Division Director; DEPI, Division of Epidemiology; DFO, Designated Federal Officer; DOD, Deputy Office Director; DMAMES, Division of Mitigation Assessment and Medication Error Surveillance; DPMH, Division of Pediatrics and Maternal Health; DPV, Division of Pharmacovigilance; IAMA, Integrated Assessment of Marketing Applications; Lit Rev, Literature Reviewer; OCOMM, Office of Communications; OD, Office Director; OPQ, Office of Pharmaceutical Quality; ORP, Office of Regulatory Policy; OSE, Office of Surveillance and Epidemiology; Rev, Reviewer; RPM, Regulatory Project Manager; Safety Eval, Safety Evaluator

27.1. Reviewer Signatures

Table 26. Signatures of Reviewers

See next page.

Table 26. Signatures of Reviewers

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Primary Reviewer	Signature: Robert J. Bahde -S			Digitally signed by Robert J. Bahde -S Date: 2023.03.22 10:22:21 -04'00'
	Comments Recommendation to Signatory (if any):	N/A		
Interdisciplinary Scientist	Robert Bahde	OND/ONPD/DNPDI	☐ Benefit Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information & (Section 23)	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Team Leader	Signature: Kevin Lorick -S			Digitally signed by Kevin Lorick -S Date: 2023.03.27 16:52:56 -04'00'
	Comments Recommendation to Signatory (if any):	An applicable recommendation from the IDS requires submission of agreed upon labeling by Sponsor. As noted in this review, IDS will provide a separate review with a final recommendation following label negotiations with Sponsor and submission of the final proposed labels.		
Interdisciplinary Scientist	Kevin Lorick	OND/ONPD/DNPDI	☐ Benefit Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information & (Section 23)	☐ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☒ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Primary Reviewer	Signature: Millie Shah -S			Digitally signed by Millie Shah -S Date: 2023.03.22 11:46:48 -04'00'
	Comments or Recommendation to Signatory (if any):	N/A		
Human Factors	Millie Shah	OSE/OMEPRM/ DMEPAII	☒ Benefit Risk Assessment (Section 2.2) ☒ Interdisciplinary Assessment (Sections 3.1.2, 7.7.4, 7.7.5) ☒ Additional Information & (Section 12.3)	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

¹ Include sections authored or contributed (e.g., 5, 5.1, 7.2, 14.2)

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Team Leader	Signature: Colleen L. Little -S			Digitally signed by Colleen L. Little -S Date: 2023.03.22 11:54:20 -04'00'
	Comments or Recommendation to Signatory (if any):	N/A		
Human Factors	Colleen Little	OSE/OMEPRM/ DMEPAII	☒ Benefit Risk Assessment (Section 2.2) ☒ Interdisciplinary Assessment (Sections 3.1.2, 7.7.4, 7.7.5) ☒ Additional Information & (Section 12.3)	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Associate Director	Signature: Lolita G. White -S			Digitally signed by Lolita G. White -S Date: 2023.03.24 12:29:29 -04'00'
	Comments or Recommendation to Signatory (if any):	N/A		
Human Factors	Lolita Sterrett	OSE/OMEPRM/ DMEPAII	☒ Benefit Risk Assessment (Section 2.2) ☒ Interdisciplinary Assessment (Sections 3.1.2, 7.7.4, 7.7.5) ☒ Additional Information & (Section 12.3)	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Deputy Director	Signature: Chi-ming Tu -S			Digitally signed by Chi-ming Tu -S Date: 2023.03.22 13:39:09 -04'00'
	Comments or Recommendation to Signatory (if any):	N/A		
DMEPA	Chi-Ming (Alice) Tu	OSE/OMEPRM/ DMEPAII	☒ Benefit Risk Assessment (Section 2.2) ☒ Interdisciplinary Assessment (Sections 3.1.2, 7.7.4, 7.7.5) ☒ Additional Information & (Section 12.3)	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

¹ Include sections authored or contributed (e.g., 5, 5.1, 7.2, 14.2)

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory	
Chemist	Signature: Joyce Crich -S Digitally signed by Joyce Crich -S Date: 2023.03.27 11:22:57 -04'00' on behalf of Sarah Zimmermann				
	Comments or Recommendation to Signatory (if any):	N/A			
CMC	Sarah Zimmermann	OPQ/OLDP/DPMAI/PMB1	☐ Benefit Risk Assessment ☒ Interdisciplinary Assessment (Section 9) ☒ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable	

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory	
Sr. Product Quality Assessor	Signature: Joyce Crich -S Digitally signed by Joyce Crich -S Date: 2023.03.27 11:29:10 -04'00'				
	Comments or Recommendation to Signatory (if any):	N/A			
CMC	Joyce Crich	OPQ/OLDP/DPMAI/PMB3	☐ Benefit Risk Assessment ☐ Interdisciplinary Assessment (Section 9) ☒ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable	

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory	
Branch Chief	Signature: Ramesh Raghavachari -S Digitally signed by Ramesh Raghavachari -S Date: 2023.03.27 10:53:33 -04'00'				
	Comments or Recommendation to Signatory (if any):	N/A			
CMC	Ramesh Raghavachari	OPQ/OLDP/DPMAI/PMB1	☐ Benefit Risk Assessment ☒ Interdisciplinary Assessment (Section 9) ☒ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable	

¹ Include sections authored or contributed (e.g., 5, 5.1, 7.2, 14.2)

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Bio Medical Engineer	Signature: Kyran R. Gibson -  Digitally signed by Kyran R. Gibson -S Date: 2023.03.27 16:42:48 -04'00'			
	Comments or Recommendation to Signatory (if any):	N/A		
CDRH	Kyran Gibson	CDRH/OPEQ/ OHTIII/DHTIIIC	☐ Benefit Risk Assessment ☒ Interdisciplinary Assessment <i>(Section 9.1)</i> ☐ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Assistant Director	Signature: 			
	Comments or Recommendation to Signatory (if any):	N/A		
CDRH	Alan Stevens	CDRH/OPEQ/ OHTIII/DHTIIIC	☐ Benefit Risk Assessment ☒ Interdisciplinary Assessment <i>(Section 9.1)</i> ☐ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Reviewer	Signature: Chibueze Ihunnah -S  Digitally signed by Chibueze Ihunnah -S Date: 2023.03.23 14:28:39 -04'00'			
	Comments or Recommendation to Signatory (if any):	N/A		
Nonclinical	Chibueze Ihunnah	OND/ONPD/ NPDPST	☐ Benefit Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information & <i>(Section 13)</i>	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

¹ Include sections authored or contributed (e.g., 5, 5.1, 7.2, 14.2)

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Staff Director	Signature: Jane J. Sohn -S			Digitally signed by Jane J. Sohn -S Date: 2023.03.24 11:14:09 -04'00'
	Comments or Recommendation to Signatory (if any):	N/A		
Nonclinical	Jane Sohn	OND/ONPD/ NPDPTS	☐ Benefit Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information & (section 13)	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Associate Director for Therapeutic Review	Signature: Celia J. Winchell -S			Digitally signed by Celia J. Winchell -S Date: 2023.03.28 12:18:51 -04'00'
	Comments or Recommendation to Signatory (if any):	N/A		
Rx Clinical/DAAP	Celia Winchell	OND/ON/DAAP	☒ Benefit Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Reviewer	Signature: Paul R. Jones -S			Digitally signed by Paul R. Jones -S Date: 2023.03.27 17:46:29 -04'00'
	Comments or Recommendation to Signatory (if any):	N/A		
Social Science	Paul Jones	OND/ONPD/ DNPDI	☐ Benefit Risk Assessment ☒ Interdisciplinary Assessment (Section 6.3.2) ☐ Additional Information	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

¹ Include sections authored or contributed (e.g., 5, 5.1, 7.2, 14.2)

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Regulatory Project Manager	Signature: Phong T. Pham -S	Digitally signed by Phong T. Pham -S Date: 2023.03.22 10:02:34 -04'00'		
	Comments or Recommendation to Signatory (if any):	N/A		
Regulatory	Phong Pham	OND/ORO/ DRO-NPD	☐ Benefit Risk Assessment ☐ Interdisciplinary Assessment ☒ Additional Information & (section 12.2)	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
CPMS	Signature: Daniel Brum -S4	Digitally signed by Daniel Brum -S4 Date: 2023.03.22 21:58:49 -04'00'		
	Comments or Recommendation to Signatory (if any):	N/A		
Regulatory	Dan Brum	OND/ORO/ DRO-NPD	☐ Benefit Risk Assessment ☐ Interdisciplinary Assessment ☐ Additional Information & (Section 12.2)	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Reviewer	Signature: Dorothy Chang -S	Digitally signed by Dorothy Chang -S Date: 2023.03.24 13:14:47 -04'00'		
	Comments or Recommendation to Signatory (if any):	N/A		
Clinical/DNPD	Dorothy Chang	OND/ONPD/ DNPDI	Benefit Risk Assessment (Section 1, 2.1) Interdisciplinary Assessment (Section 3, 6.3.3, 7.2 – 7.6, 7.7.1 – 7.7.2, 8.3, 8.4, 11) Additional Information & (Section 12.1, 12.4, 17)	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

¹ Include sections authored or contributed (e.g., 5, 5.1, 7.2, 14.2)

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Cross-Disciplinary Team Lead	Signature: Jody E. Green -S Digitally signed by Jody E. Green -S Date: 2023.03.24 13:39:46 -04'00'			
	Comments or Recommendation to Signatory (if any):	N/A		
Clinical/DNPD	Jody Green	OND/ONPD/ DNPDI	☒ Benefit Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Division Director	Signature: Rigoberto A. Roca -S Digitally signed by Rigoberto A. Roca -S Date: 2023.03.28 04:50:32 -04'00'			
	Comments or Recommendation to Signatory (if any):	N/A		
Rx Clinical/DAAP	Rigoberto Roca	OND/ON/DAAP	☒ Benefit Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Division Director	Signature: Nushin Todd -S Digitally signed by Nushin Todd -S Date: 2023.03.27 18:00:31 -04'00'			
	Comments or Recommendation to Signatory (if any):	N/A		
Clinical/DNPD	Nushin Todd	OND/ONPD/ DNPDI	☒ Benefit Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

¹ Include sections authored or contributed (e.g., 5, 5.1, 7.2, 14.2)

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Office Director (Acting)	Signature: Teresa Buracchio -S	Digitally signed by Teresa Buracchio -S Date: 2023.03.28 07:26:13 -04'00'		
	Comments or Recommendation to Signatory (if any):	N/A		
Rx Clinical/ON	Teresa Buracchio	OND/ON	☒ Benefit Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

Discipline	Reviewer Name	Office/Division	Sections Authored/ Contributed/Approved ¹	Recommendation to Signatory
Office Director	Signature: Theresa M. Michele -S	Digitally signed by Theresa M. Michele -S Date: 2023.03.28 11:21:18 -04'00'		
	Comments or Recommendation to Signatory (if any):	N/A		
Clinical/ONPD	Theresa Michele	OND/ONPD	☒ Benefit Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information &	☒ Based on my assessment of the application, no deficiencies preclude approval ☐ Based on my assessment of the application, there are deficiencies that preclude approval ☐ Not Applicable

¹ Include sections authored or contributed (e.g., 5, 5.1, 7.2, 14.2)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHONG T PHAM
03/28/2023 02:15:25 PM

JODY E GREEN
03/28/2023 02:27:39 PM

TERESA J BURACCHIO
03/28/2023 02:50:33 PM

THERESA M MICHELE
03/28/2023 05:39:03 PM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION –
POSTMARKETING REQUIREMENT (PMR 3707-1)**

Application number: NDA 208411

Supporting document/s: 454, 659

Applicant's letter date: July 30, 2020; October 24, 2022

CDER stamp date: July 30, 2020; October 24, 2022

Product: Narcan (Naloxone Hydrochloride)

Indication: For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression

Applicant: Emergent Operations Ireland LTD

Pharm/Tox Division: Division of Pharm/Tox for Neuroscience (DPT-N)

Reviewer: Alexander I. Son, PhD

Supervisor: Newton H. Woo, PhD

Deputy Division Director: R. Daniel Mellon, PhD

Clinical Review Division: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Clinical Division Director: Rigoberto Roca, MD

Project Manager: Kimberly Compton, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 208411 are owned by Emergent Operations Ireland LTD or are data for which Emergent Operations Ireland LLC has obtained a written right of reference. Any information or data necessary for approval of NDA 208411 that Emergent Operations Ireland LTD does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208411.

1 Executive Summary

1.1 Introduction

The current submission is in response to a postmarketing requirement (PMR) issued in Supplement 2 of NDA 208411 for NARCAN Nasal Spray dated September 23, 2019. Supplement 2 was regarding proposed changes to the drug product formulation (b) (4) and a change in the secondary container closure system (b) (4).

(b) (4) Concerns were originally raised as to whether volatiles of the secondary container closure system may be able to leach into the drug product. However, as the proposed product is for a life-saving indication and that the proposed change represents a minimal change to the container closure system, an extractables assessment of the secondary container closure system was issued as a PMR to the Applicant:

3707-1 Conduct an extractables assessment of the secondary container closure system, including the newly proposed (b) (4) to determine if any volatile compounds could be released from the secondary container closure system. Provide a risk assessment for any compound detected at greater than or equal to 5 mcg/day.

1.2 Brief Discussion of Nonclinical Findings

The Sponsor has submitted extractables testing for the secondary container closure system to address PMR 3707-1. A toxicological risk assessment was provided for extractables (b) (4) that exceeded a maximum daily exposure of 5 mcg/day.

It was noted in the cover letter that the Applicant intended to utilize a new (b) (4) (b) (4) from the one that was currently submitted. It was further stated in annual report 6 (SDN 609) (b) (4). However, it was unclear as to whether this was (b) (4). The following information request (IR) was sent on October 18, 2022 requesting further clarification as to this new (b) (4).

We acknowledge your plans to implement a new (b) (4) for your secondary container closure system as this is particularly relevant for PMC 3707-1 and your planned Rx to OTC switch. However, it is unclear from your submissions (SDN 454; SDN 609 ANRPT-6) regarding which (b) (4) will be used for your container closure system of your planned OTC product (Suppl-6). Clarify the status of the new (b) (4) with timelines, and indicate whether the new (b) (4) will solely be used in the OTC product. Provide this information COB Friday October 21, 2022.

In the Applicant response on October 24, 2022, the Applicant provided an update on the status of the new (b) (4). The Applicant stated that Aptar, the manufacturer of the unit dose device, discontinued (b) (4) and replaced it with a new (b) (4). The implementation and data (b) (4) was reported in SDN 609, and it is currently being used in the marketed NARCAN Nasal Spray since April 2021.

Reviewer Comment: *The Applicant submitted an extractables report of the new (b) (4) under SDN 609 that evaluated (b) (4). The post-marketing CMC team reviewed this extraction report and has determined that the methods utilized were adequate. No extractables were observed above the specified AET that was based on a 5 mcg/day threshold (See CMC review by Sara Zimmermann dated February 13, 2023 for further details). Given the absence of detectable extractables above the AET, there are no safety concerns regarding the new (b) (4) utilized in the container closure system.*

1.3 Recommendations

Because the component in the secondary container closure system for which the PMR was issued for is no longer in use, the original PMR 3707-1 can be released. Further, because the subsequently submitted data for the new (b) (4) does not raise any safety concerns, a new PMR does not need to be issued.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALEXANDER I SON
03/03/2023 09:32:22 AM

NEWTON H WOO
03/03/2023 09:34:22 AM

RICHARD D MELLON
03/03/2023 10:01:20 AM