CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217722Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217722
Priority or standard	Priority
Submit date(s)	10/28/2022
Received date(s)	10/28/2022
PDUFA goal date	7/28/2023
Division/office	Division of Non-Prescription Drugs I (DNPDI)
Review completion date	7/21/2023
Established/proper name	Naloxone hydrochloride
(Proposed) proprietary name	RiVive
Pharmacologic class	Opioid reversal agent
Other product name(s)	HRT001
Applicant	Harm Reduction Therapeutics, Inc.
Dosage form(s)/formulation(s)	Intranasal 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)	Emergency treatment of opioid overdose/Adults and children
SNOMED CT code for proposed indication disease term(s)[1]	242253008, Opiate Overdose
Regulatory action	Approval
Approved dosage (if applicable)	3 mg/0.1 mL
Approved indication(s)/ population(s) (if applicable)	As above
SNOMED CT code for approved indication disease term(s)[1]	As above

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AAPCC	American Association of Poison Control Centers
AE	adverse event
AET	analytical evaluation threshold
ANDA	abbreviated new drug application
AUC	area under the plasma concentration-time curve
BA	bioavailability
CC	close call
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CONFER	Comprehension for OTC Naloxone
COVID-19	coronavirus disease 2019
COWS	Clinical Opiate Withdrawal Scale
DFL	drug facts label
DMEPA II	Division of Medication Error Prevention and Analysis II
DMF	drug master file
DNPD I	Division of Nonprescription Drugs I
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FR	Federal Register
HCl	hydrochloride
HCP	healthcare professional
HFVS	human factors validation study
HRT	Harm Reduction Therapeutics
ICH	International Council for Harmonisation
IM	intramuscular(ly)
IN	intranasal(ly)
IND	investigational new drug
IV	intravenous(ly)
LB	lower bound
LCS	label comprehension study
MDD	maximum dry density
MedDRA	Medical Dictionary for Regulatory Activities
NAL	naloxone access laws
NDA	new drug application
NHANES	U.S. National Health and Nutrition Examination Survey
NNS	Narcan nasal spray
NPD-PTS	Nonprescription Drugs and Pharmacology and Toxicology Staff
NPDS	National Poison Data System
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSIS	Office of Study Integrity and Surveillance

OTS	Office of Translational Sciences
PDP	principal display panel
PDUFA	Prescription Drug User Fee Act
PI	prescribing information
PK	pharmacokinetic
P/T	pharmacology/toxicology
PT	preferred term
(Q)SAR	Quantitative Structure Activity Relationship
QSG	Quick Start Guide
QT	qualification threshold
R	reference product
RNA	ribonucleic acid
RRT	relative retention time
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SD	standard deviation
SOI	statement of identity
T	test product
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TTC	threshold of toxicological concern
UD	use difficulty
UE	use error
WHO	World Health Organization

I. Executive Summary

1. Summary of Regulatory Action

Harm Reduction Therapeutics, Inc., (HRT, "the Applicant") submitted new drug application (NDA) 217722 for RiVive (naloxone hydrochloride) nasal spray on October 28, 2022, in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

RiVive is a single-use, drug-device combination product that delivers naloxone hydrochloride 3 mg/0.1 mL intranasally. The proposed use is to "revive someone during an overdose from many prescription pain medications or street drugs such as heroin." RiVive is intended for community use, to be administered by individuals without medical training (i.e., laypeople) in community settings without the need for additional supplies or assembly before use. The Applicant proposes to market RiVive as a direct-to-nonprescription product for use in adults and children of all ages.

Opioid overdose is a major public health problem in the United States, leading to tens of thousands of deaths every year. There is only one approved nonprescription naloxone product, which was approved by FDA on March 29, 2023, and is not yet marketed at the time of this writing. Prescription naloxone products are frequently obtained without patient-specific prescriptions, either through community-based naloxone distribution programs or through state naloxone access laws (NALs). However, despite implementation of state NALs, opioid overdose deaths continue to climb. It is noted 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 nonprescription naloxone products is anticipated to address some of these obstacles to broader naloxone access and, thereby, help combat the opioid crisis.

Although 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 and without the supervision of a healthcare professional, safely and effectively administer naloxone relying only on the labeling (87 FR 68702, November 16, 2022). Community-based naloxone distribution programs may provide supplies (e.g., syringes, atomizers, or instructions for use) as part of a naloxone kit as well as patient counseling on how to use naloxone. Additionally, some state NALs and collaborative agreements require pharmacists to provide instruction to those purchasing naloxone. Thus, naloxone distribution via community-based naloxone programs and NALs is not the same as naloxone having nonprescription status, where a naloxone product may be purchased without any additional instruction other than the product's labeling.

In this NDA, the Applicant submitted comparative bioavailability (BA) data referencing the prescription product approved under NDA 016636 (Narcan [naloxone hydrochloride] 0.4 mg/mL injection) to support clinical efficacy as well as systemic safety of the proposed product. In the pivotal comparative BA study, RiVive demonstrated sufficient systemic absorption of naloxone

as well as rapidity of onset compared to the listed drug, particularly in the early critical period after drug administration. To support the safety of RiVive's new formulation and the different route of administration compared with the listed drug, the Applicant evaluated the potential for local toxicity in its comparative BA studies. To support the use of RiVive in the pediatric population, the Applicant submitted a pediatric assessment that was supported by the published literature. Additionally, the Applicant submitted analyses of 7 years of pharmacovigilance safety data related to intranasal (IN) naloxone use from three databases and a comprehensive review of the published literature.

To support the nonprescription use of this product, the Applicant used FDA's model naloxone drug facts label (DFL) as the foundation of its proposed DFL. The model naloxone DFL was tested and validated in a pivotal label comprehension study (LCS) conducted among a wide range of potential nonprescription naloxone users (84 FR 8728, March 11, 2019). Product-specific instructions were added to the DFL and evaluated in a simulated-use human factors validation study (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. [1]

During the review, a number of chemistry, manufacturing, and controls (CMC) issues were identified by the team; however, these have all been addressed as summarized in this review.

Reflecting the importance of this product from the public health perspective and the lack of approved nonprescription options, FDA granted the investigational new drug (IND) application 134611 a Fast Track designation on July 1, 2022, and rolling submission and review on July 27, 2022. This NDA was granted priority review status on December 23, 2022. During the review cycle, a major amendment was received on February 17, 2023, thus extending the original goal date by 3 months.

This NDA was reviewed by a multidisciplinary review team consisting of members from the Division of Nonprescription Drugs I (DNPD I), the Division of Anesthesiology, Addiction Medicine, and Pain Medicine, the Office of Clinical Pharmacology, the Division of Maternal and Pediatric Health, the Office of Pharmaceutical Quality, the Nonprescription Drugs Pharmacology and Toxicology Staff (NPD-PTS), and the Division of Medication Error Prevention and Analysis II (DMEPA II). 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 the benefit-risk framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Interdisciplinary Assessment document and the Product Quality Review.

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

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. • The U.S. Department of Health and Human Services declared the opioid crisis a public health emergency in 2017 and has renewed the declaration multiple times since the initial declaration (Administration for Strategic Preparedness & Response 2023). • 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 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 could potentially be administered by individuals without medical training (laypeople) because they do not require additional supplies or assembly prior to use.	• 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 another nonprescription naloxone product broadens the nonprescription armamentarium, which may address some of the current barriers to accessing naloxone and increase 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. Many feature provisions to allow for nonpatient-specific prescriptions or the prescribing of naloxone to someone not directly at risk of overdose, and some 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). • 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 an 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). • Currently, there is only one approved nonprescription naloxone product. • Nalmefene hydrochloride is an alternative prescription opioid antagonist with a longer duration of action than naloxone. Nalmefene is available for intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration, which are primarily used in hospital settings. A prescription nasal spray dosage form was first approved in May 2023 for healthcare and community use.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• RiVive demonstrated sufficient systemic absorption of naloxone as well as rapidity of onset compared to an approved naloxone product, including in the early critical period after drug administration. A single dose of RiVive demonstrated systemic exposures that are roughly similar to 1.3 mg IM naloxone, which falls within the approved initial dosing range for injectable naloxone. • Postmarketing distribution information shows a large amount of intranasal (IN) naloxone distribution and it comprises the majority of prescription naloxone dispensed (see OSE Consult Review dated February 27, 2023; DARRTS Reference ID: 5131876). • Evidence for the effectiveness of IN naloxone may also be supported by the small number of postmarketing reports of "limited efficacy" among cases reporting IN naloxone use in the community setting. • In a pivotal label comprehension study, general consumers and opioid users demonstrated adequate comprehension of critical labeling information on the FDA model naloxone DFL. Individuals with limited literacy and adolescents also performed adequately.	• The available data provide substantial evidence to support the effectiveness of RiVive in the treatment of opioid overdose in the adult and pediatric population. • RiVive is expected to be effective as a nonprescription product as supported by findings of the pivotal label comprehension study.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The safety data from RiVive's clinical program showed most adverse events were mild and self-limited. Most adverse events were related to IN examination findings that were not associated with subjective symptoms, making the clinical significance of the exam findings unclear. • 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 naloxone-induced precipitated withdrawal, pulmonary edema, seizures, and device use errors associated with IN naloxone use. Few serious adverse events were found among pediatric or geriatric patients. 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 and naloxone's known side effect profile. • The human factors validation study (HFVS) demonstrated use errors related to hand positioning on the device and pressing the plunger, administrations of the product to the mouth, delays in calling 911, and administration of both doses of naloxone at one time or thinking that a device contained more than one spray.	• There were no serious adverse events or significant safety findings from the clinical program for RiVive. • 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. • Changes to the DFL and labeling will be recommended to help mitigate use errors noted in the HFVS; these recommendations will also help align the proposed labeling with labeling from the approved nonprescription naloxone nasal spray.

Abbreviations: DFL, drug facts label; NAL, naloxone access law; HFVS, human factors validation study

2.2. Conclusions Regarding Benefit-Risk

Opioid overdose is a major public health problem in the United States. RiVive's approval will increase nonprescription naloxone options and the overall availability of this life-saving drug for general consumers.

The submitted information supports that RiVive has met the evidentiary standards for approval of a novel naloxone product. In its comparative BA study, RiVive demonstrated adequate systemic absorption of naloxone as well as rapidity of onset compared to an approved naloxone product, including in the early critical period after drug administration. A single dose of RiVive demonstrated systemic exposures that are roughly similar to 1.3 mg IM naloxone, which falls within the approved initial dosing range for injectable naloxone (0.4 to 2 mg) and supports clinical efficacy as well as systemic safety of the proposed product. No serious adverse events or significant safety findings were identified in the review. The most common adverse events noted in the clinical pharmacology program included self-limited nasal exam findings, such as mucosal erythema and nasal congestion as well as dysgeusia. The findings supported local safety of this new IN naloxone formulation. Pediatric use of the proposed product's dose, dosage volume, and delivery device is supported in the Applicant's pediatric assessment. Notably, the dosage volume and delivery device are the same as those utilized in other IN naloxone products, which are also approved for the full pediatric age range. The Applicant's review of the postmarketing safety data spanned the years since initial approval of an IN naloxone product and demonstrated no new or unexpected safety findings that would preclude approval. This finding was confirmed in FDA's evaluation of the postmarketing safety data in the FDA Adverse Event Reporting System (FAERS).

To support nonprescription use of the product, the Applicant developed its DFL based on FDA's model naloxone DFL, which was validated for comprehension in a pivotal LCS and published in a 2019 Federal Register (FR) notice. In order to rely on FDA's pivotal LCS results, the only modifications made to the model naloxone DFL were related to RiVive's product-specific information. The Applicant conducted a simulated-use HFVS to demonstrate usability of the user interface. The HFVS results demonstrated use-related issues with some critical tasks. Some examples of use errors or difficulties included issues related to correct hand and finger positioning for drug administration, use errors related to administration of the drug into the mouth, and use errors related to misinterpreting the number of doses per nasal spray device. Reviewers from DMEPA II have recommended changes to the user interface to mitigate residual risks. These recommendations are carefully targeted to address root causes of use errors.

In most cases, FDA expects that post-study modifications to the labeling would undergo repeat human factors testing to confirm that the changes are effective and do not introduce new risks. However, this specific issue was discussed at a recent advisory committee meeting held in February 2023 for the nonprescription application of Narcan nasal spray. The panel considered the benefit-risk profile of naloxone, the strength of FDA's label comprehension study conducted to support the foundational model naloxone DFL, and the changes FDA recommended to the labeling. The panel unanimously concluded that additional human factors testing was not recommended. In this instance, where the benefit-risk is heavily in favor of the benefit of a drug, a strongly supportive LCS had already been conducted, and some supportive information had been collected in a HFVS, additional human factors testing was not required to support the

incremental benefit of additional labeling modifications. Notably, many of the labeling revisions recommended by the review team for RiVive are intended to align RiVive's labeling with that approved for Narcan nasal spray. Additionally, the changes recommended by DMEPA II for RiVive's user interface pose a low likelihood of introducing new risks during product use, and therefore can be implemented without submitting additional HFVS data.

During the review cycle, the review team identified several CMC issues, including:

1. The Applicant's lack of a drug substance supplier because its originally contracted supplier ceased manufacturing naloxone hydrochloride, resulting in an incomplete drug substance supply chain
2. The Applicant's drug product manufacturer, Catalent Pharma Solutions, being in an Official Action Indicated status at the time of application submission
3. The inadequacy of the microbiology data to support a proposed drug product that is aqueous (b) (4)
4. Concerns about the adequacy of the information to support the proposed shelf-life of 36 months

All CMC issues have now been addressed. The Applicant has addressed the lack of a drug substance supplier by securing enough drug substance from its originally contracted supplier to support the commercial manufacture of the drug product for several years and will identify an alternative drug substance manufacturer post-NDA approval. The drug product manufacturer was found to be acceptable after a good manufacturing practice inspection. Additional data from a growth promotion study that were generated and submitted during the review cycle were considered adequate to address microbiological concerns. Stability testing was found to support an expiry of 36 months. There are no outstanding CMC issues that preclude approval.

The benefit-risk profile adequately supports the approval of RiVive as a nonprescription treatment for opioid overdose.

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 and 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 intravenously (IV), intramuscularly (IM), or subcutaneously (SC).

RiVive is a single-use, drug-device combination product that delivers naloxone hydrochloride 3 mg/0.1 mL intranasally. The proposed use is to "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin. RiVive was designed for use in nonhealthcare settings by laypeople to reverse the effects of an opioid overdose. The Applicant proposes to market RiVive as a nonprescription product for use in patients of all ages. The proposed dosing regimen is one spray into one nostril; repeat doses may be given, using a new nasal spray device, every 2 to 3 minutes until the person wakes up. The Applicant plans to package RiVive in a carton containing two single-use sprays.

Therapeutic Context: Analysis of Condition

Opioid overdose is a serious condition that is characterized by life-threatening respiratory and central nervous system (CNS) depression. If not immediately treated, opioid overdose may lead to significant morbidity and mortality due to irreversible hypoxic injury. The opioid crisis, which encompasses misuse, abuse, and overdose deaths involving illicit and prescription opioids, was initially declared a public health emergency in 2017. The declaration has been renewed multiple times since the initial declaration (Administration for Strategic Preparedness & Response 2023). Opioid overdose can occur in patients who take prescription opioid medication, in household contacts of the patient, and in people who misuse or abuse opioids. Nationally, deaths from opioid overdose totaled 80,997 in 2021 (Ahmad et al. 2023).

Therapeutic Context: Analysis of Current Treatment Options

Injectable naloxone for IV, IM, and SC administration was approved for prescription use in the United States in 1971. Since then, several strengths, dosage forms, and presentations of naloxone have been approved; all but one naloxone product are available by prescription only. Narcan nasal spray was recently approved for nonprescription use on March 29, 2023. Table 3 lists approved single-ingredient naloxone drug products.

Table 3. Currently Approved Single-Ingredient Naloxone Products[1]

Proprietary Name	NDA	Approval Date	Dosage Form or Presentation	Dose	Route
Narcan	016636	Apr 13, 1971[2]	Solution for injection	0.4–2 mg	IV, IM, SC
Evzio	205787	Apr 3, 2014	Autoinjector	0.4 mg	IM, SC
Narcan Nasal Spray	208411	Nov 18, 2015	Nasal spray	4 mg	IN

Proprietary Name	NDA	Approval Date	Dosage Form or Presentation	Dose	Route
Evzio	209862	Oct 19, 2016	Autoinjector	2 mg	IM, SC
Narcan Nasal Spray	208411, S001	Jan 24, 2017[2]	Nasal spray	2 mg	IN
Kloxxado	212045	Apr 29, 2021	Nasal spray	8 mg	IN
Zimhi	212854	Oct 15, 2021	Prefilled syringe	5 mg	IM, SC
Naloxone hydrochloride autoinjector[3]	215457	Feb 28, 2022	Autoinjector	10 mg	IM, SC
Naloxone hydrochloride nasal spray	208969	Mar 7, 2023	Nasal spray	4 mg	IN

Source: Reviewer summary
[1] This table does not include approved generic naloxone products
[2] Product withdrawn not for reasons of safety or effectiveness
[3] 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, and more recently as an intranasal (IN) product. Like naloxone, it carries cardiovascular risks, and there is a risk of precipitated withdrawal. However, its duration of action is longer than that of naloxone, and its safety and effectiveness have not been established in pediatric patients.

Clinical Development Program

The Applicant conducted the clinical development program under investigational new drug (IND) application 134611. An initial meeting was held between Mundipharma Research Limited to discuss development of a prescription naloxone nasal spray product. Subsequently, Harm Reduction Therapeutics (HRT) acquired the IND and an additional six meetings were held, including two milestone meetings for the development of a nonprescription product. Key discussion points included the data necessary to demonstrate sufficient systemic absorption of naloxone as well as rapidity of onset from RiVive compared to a listed drug, the clinical safety data necessary to support the proposed product, the development of the product labeling and necessary data to support the product's nonprescription use, and the expected contents of the NDA from a chemistry, manufacturing, and controls (CMC), nonclinical, and postmarketing safety perspective.

Further information on key meetings, dates, and discussion points are provided in greater detail in Section 12.

Regulatory History

Reflecting the importance of this product from the public health perspective and the lack of approved nonprescription options, FDA granted the application a Fast Track designation on July 1, 2022, rolling submission and review on July 27, 2022, and a priority review designation on December 23, 2022. During the review cycle, an amendment to the application was received on February 17, 2023, containing extensive new device-related risk assessment information, which constituted a major amendment. Thus, the original goal date was extended by 3 months.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Clinical Pharmacology Data Support Reliance on FDA's Previous Findings of Safety and Efficacy for NDA 016636

Refer to Section 6.3.1.

3.1.1.2. Drug Facts Label and Pictograms are Well Comprehended by Consumers

Refer to Section 6.3.2.

3.1.2. Key Safety Review Issues

3.1.2.1. Clinical Safety of the Proposed Product

Refer to Section 7.7.1.

3.1.2.2. Adverse Events From Postmarketing Safety Data Associated With Use of Approved Intranasal Naloxone Products

Refer to Section 7.7.2.

3.1.2.3. Limitations of Human Factors Validation Study Methodology

Refer to Section 7.7.3.

3.1.2.4. Qualitative Human Factors Validation Study Findings

Refer to Section 7.7.4.

3.2. Approach to the Clinical Review

To support efficacy of the proposed product, the Applicant relied on the established efficacy of an approved naloxone product by demonstrating similar or increased bioavailability (BA) of its proposed product compared with the reference drug, Narcan injectable solution (NDA 016636). The Applicant conducted two relative BA studies (HRT001-PK01 and HRT001-PK02) in healthy adult subjects. Study HRT001-PK02 is considered the pivotal relative BA study

supporting efficacy of RiVive; see Section 6 for a high-level summary and Section 14 for a full review.

The safety of the proposed product is supported by the clinical safety data generated from the relative BA studies HRT001-PK01 and HRT001-PK02 (see Section 7.6.1). In addition, the Applicant provided analyses of postmarketing safety data related to IN naloxone use from FDA Adverse Event Reporting System (FAERS), World Health Organization (WHO) VigiBase, American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS), and the published literature spanning a 7-year period from January 1, 2015, through December 31, 2021 (see Section 7.6.2.2).

FDA has also conducted an independent review of FAERS and the published literature for adverse events (AEs) related to IN naloxone 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; see Section 7.6.2.3).

To support the nonprescription use of RiVive, the Applicant developed packaging and labeling for its proposed nonprescription product. The Drug Facts label (DFL) uses FDA's model naloxone DFL, which was tested and validated in a pivotal label comprehension study (LCS) and includes additional product-specific instructions. Information supporting FDA's model naloxone DFL is reviewed in Section 6.3.2. Modifications to the DFL along with other elements of the product's user interface (i.e., packaging and additional labeling) were evaluated in a human factors validation study (HFVS) to demonstrate usability among groups of potential nonprescription users and are reviewed in Section 7.7.4.

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: Human factors validation study	Sections 7.7.3 and 7.7.4
☐	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	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

No nonclinical data were generated for the assessment of potential effectiveness.

5.2. Clinical Pharmacology / Pharmacokinetics

Because the clinical pharmacology data form the basis of effectiveness for the proposed product, see Section 6 for a high-level summary of this information and Section 14 for a full clinical pharmacology review.

6. Efficacy (Evaluation of Benefit)

Applicants proposing novel naloxone products need to demonstrate sufficient systemic absorption of naloxone as well as rapidity of onset compared to an approved naloxone product, particularly in the early critical period after drug administration. FDA has determined that clinical efficacy trials are not necessary for novel naloxone products because effective doses have already been established. Clinical efficacy trials present significant logistical and ethical challenges because approved naloxone products are already available for treatment of opioid overdose, which, if not immediately treated, could result in substantial morbidity and mortality. Therefore, historically, efficacy for new naloxone products has been based on information known about other approved naloxone products and supported by a relative BA study conducted in healthy volunteers.

In addition to the BA studies required to support their proposed naloxone doses/products, applicants may also need to provide additional data, such as literature reviews, to support the safety and effectiveness of their products if the exposure is different or substantially higher. Other studies may also be needed to support approval of the product (e.g., human factors study).

6.1. Assessment of Dose and Potential Effectiveness

Not applicable.

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

The Applicant conducted two relative BA studies for the development of the proposed product. Table 5 summarizes these studies.

Table 5. Listing of Clinical Studies

Study Identifier (Type of Study)	Objective(s) of the study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Enrolled Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
HRT001-PK01 (Phase 1, Relative BA)	Relative BA HRT001 vs. reference product	Randomized, open-label, 2-sequence, 4-period, crossover bioavailability study	Test product: IN naloxone HCl, 3 mg/0.1 mL Reference product: IM naloxone HCl, 0.4 mg/mL	38	Healthy subjects	Single dose
HRT001-PK02 (Phase 1, Relative BA)	Part I: Relative BA HRT001 vs. reference product	Randomized, open-label, 2- sequence, 4-period, crossover bioavailability study	Test product: IN naloxone HCl, 3 mg/0.1 mL Reference product: IM naloxone HCl, 0.4 mg/mL	36	Healthy subjects	Single dose
	Part II: Impact of prolonged mask wearing on relative BA of HRT001	Randomized, open-label 2- period, crossover relative bioavailability study	Treatment A: IN naloxone HCl, 3 mg/0.1 mL with prolonged mask-wearing 24 h prior to dosing Treatment B: IN naloxone HCl, 3 mg/0.1 mL without prolonged mask-wearing	24	Healthy subjects	Single dose

Source: Adapted from Applicant Submission
Abbreviations: BA, bioavailability; HCl, hydrochloride; IM, intramuscular; IN, intranasal; vs, versus

6.3. Key Efficacy Review Issues

6.3.1. Clinical Pharmacology Data Support Reliance on FDA's Previous Findings of Safety and Efficacy for NDA 016636

Background

To rely upon FDA's previous findings of systemic safety and efficacy of naloxone for NDA 016636, the Applicant needs to demonstrate sufficient systemic absorption of naloxone as well as rapidity of onset compared to the approved product, particularly in the early critical period after drug administration. The labeling of the injectable product recommends an initial dose of 0.4 to 2 mg for IV, IM, or SC administration, followed by repeated doses as needed for emergency treatment of known or suspected opioid overdose in adults. If no response is observed after 10 mg of naloxone has been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. If the Applicant can demonstrate that systemic exposure of the novel product, including in the early critical period after drug administration, falls within that of the range of 0.4 to 2 mg from the reference product in the BA study, then the Applicant may rely on FDA's previous findings of systemic safety and effectiveness of the reference product.

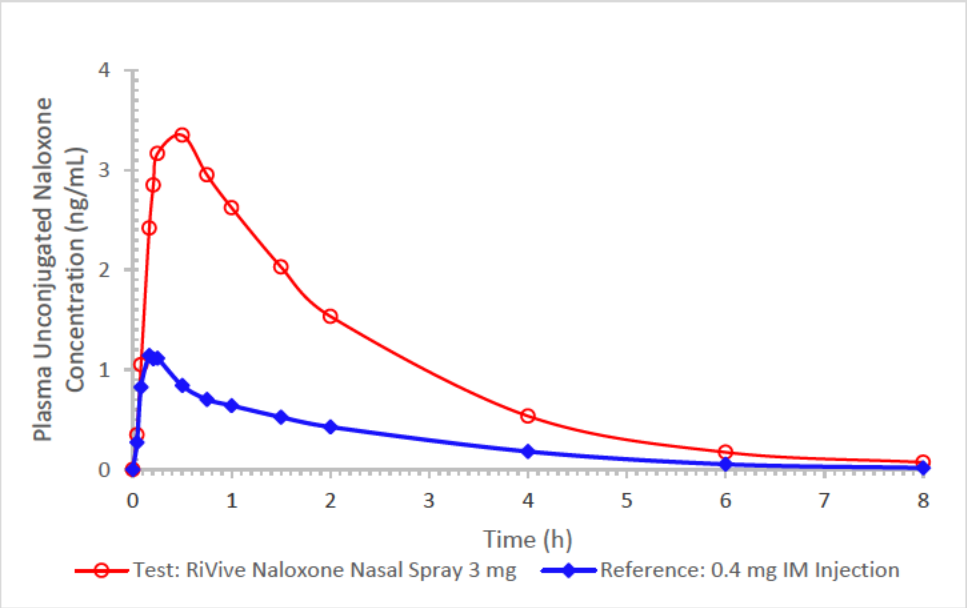
Assessment

The pivotal BA study (HRT001-PK02) comparing the 3-mg nasal spray product (test product, T) with the 0.4-mg IM naloxone hydrochloride solution (reference product, R) was used to establish efficacy and systemic safety for RiVive. Because Narcan injectable solution (NDA 016636) had been discontinued from sale,[2] the Applicant used a generic naloxone product manufactured by Hospira Inc. in the study. The study had a replicate design wherein each subject received both the test product and reference product twice.

One RiVive naloxone nasal spray administered in one nostril (i.e., 3-mg dose) demonstrated much higher systemic exposure to naloxone, in terms of the area under the plasma concentration time curve from time 0 to the time of last measurable concentration (AUC_{0-t}), AUC from time 0 to infinity (AUC_{0-inf}), and maximum plasma concentration (C_{max}), in comparison with the reference product. RiVive exhibited comparable $AUC_{0-2.5min}$ and AUC_{0-5min}, and greater $AUC_{0-10min}$ than a 0.4 mg IM naloxone dose. The naloxone plasma concentration-time profiles following IN (3-mg dose) and IM (0.4-mg dose) naloxone administration in healthy subjects from 0 to 8 hours are shown in Figure 1.

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

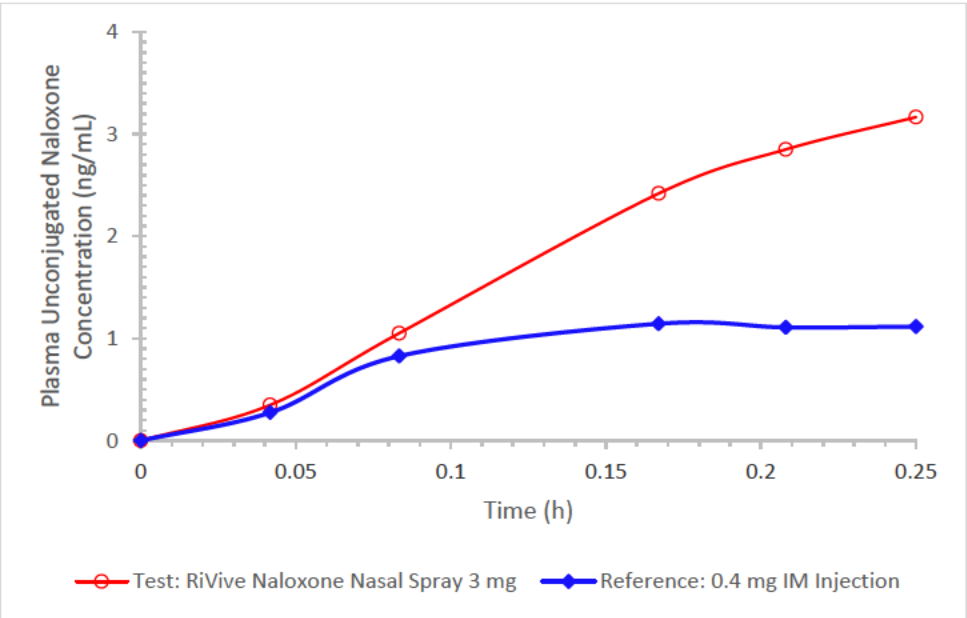
Figure 1. Mean Plasma Concentration Time Profiles of Naloxone Following 3 mg IN Administration of RiVive Naloxone HCl Nasal Spray (Test Product) vs. 0.4 mg IM Injection (Reference Product), 0 to 8 Hours



Source: Reproduced figure based on Study Report HRT001-PK02 Table 14-1
Abbreviations: HCl, hydrocholoride; IM, intramuscular; IN, intranasal

The naloxone plasma concentration-time profiles following IN (3-mg dose) and IM (0.4-mg dose) naloxone administration from 0 to 0.25 hours are shown in Figure 2.

Figure 2. Mean Plasma Concentration Time Profiles of Naloxone Following 3 mg IN Administration of RiVive Naloxone HCl Nasal Spray (Test Product) vs. 0.4 mg IM Injection (Reference Product), 0 to 0.25 Hours



Source: Reproduced figure based on Study Report HRT001-PK02 Table 14-1
Abbreviations: HCl, hydrochloride; IM, intramuscular; IN, intranasal

One spray of RiVive in one nostril (3-mg total dose) exhibited a 2.98-fold higher C_{max} and 3.25- to 3.26-fold higher AUC_{0-t} and AUC_{0-inf} compared to the reference, a single dose of 0.4 mg naloxone given via IM injection. The mean $AUC_{0-2.5min}$, AUC_{0-5min}, and $AUC_{0-10min}$ values during the early absorption phase for a single 3-mg dose of RiVive were 107%, 102%, and 142%, respectively, compared to those of a single 0.4 mg IM injection. RiVive exhibited comparable $AUC_{0-2.5min}$ and AUC_{0-5min}, and an $AUC_{0-10min}$ 42% greater than a 0.4 mg IM naloxone dose.

The labeling of the approved Narcan injectable product recommends a dose of 0.4 to 2 mg for IV, IM or SC administration. A single dose of RiVive demonstrated systemic exposures that are roughly similar to 1.3 mg IM naloxone, which falls within the approved initial dosing range for Narcan. The efficacy of the proposed product is supported by its pharmacokinetic (PK) data as compared to that of injectable Narcan.

Table 6. Statistical Analysis (Standard Average Bioequivalence) of Naloxone - IN Administration of RiVive Naloxone HCl Nasal Spray 3 mg (Test) and 0.4 mg IM Injection (Reference)

	Geometric Least Squares Means			
Parameter	RiVive Naloxone HCl Nasal Spray 3 mg (Test)	0.4 mg IM Injection (Reference)	Ratio (Test/ Reference) (%)	90% Confidence Interval
C_{max} (ng/mL)	3.6963	1.2407	297.92	263.76 – 336.51
AUC_{0-t} (ng.h/mL)	6.8482	2.1042	325.45	296.40 – 357.35
AUC_{0-inf} (ng.h/mL)	6.9821	2.1433	325.76	296.66 – 357.71
$AUC_{0-2\ 5min}$ (ng.h/mL)	0.0025	0.0023	106.89	78.85 – 144.89
AUC_{0-5min} (ng.h/mL)	0.0160	0.0157	101.51	75.88 – 135.80
$AUC_{0-10min}$ (ng.h/mL)	0.1155	0.0814	141.87	114.97 – 175.07

Source: Study Report HRT001-PK02 Table 11-3
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; HCl, hydrochloride; IM, intramuscular; IN, intranasal

Conclusion

The Applicant has established a scientific bridge to NDA 016636 by demonstrating that the proposed product has comparable or higher systemic exposure and comparable or quicker onset of action than the reference drug.

6.3.2. Drug Facts Label and Pictograms are Well Comprehended by Consumers

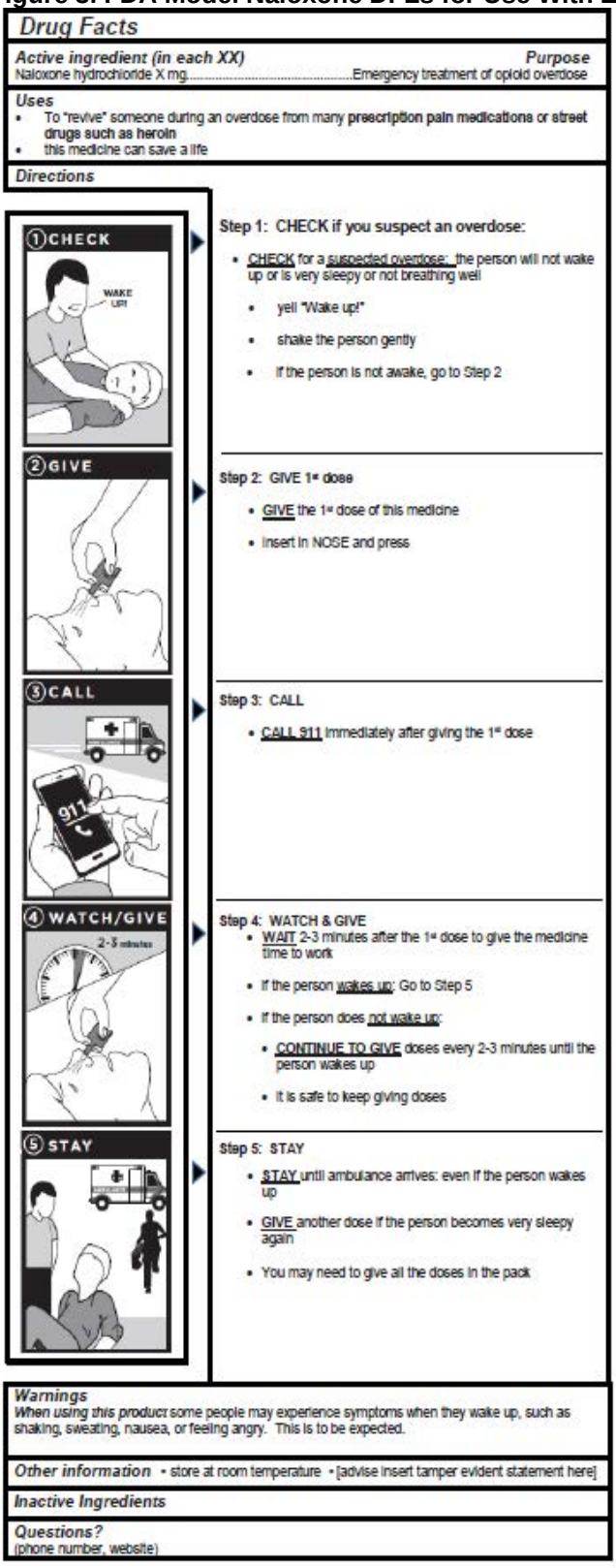
Background

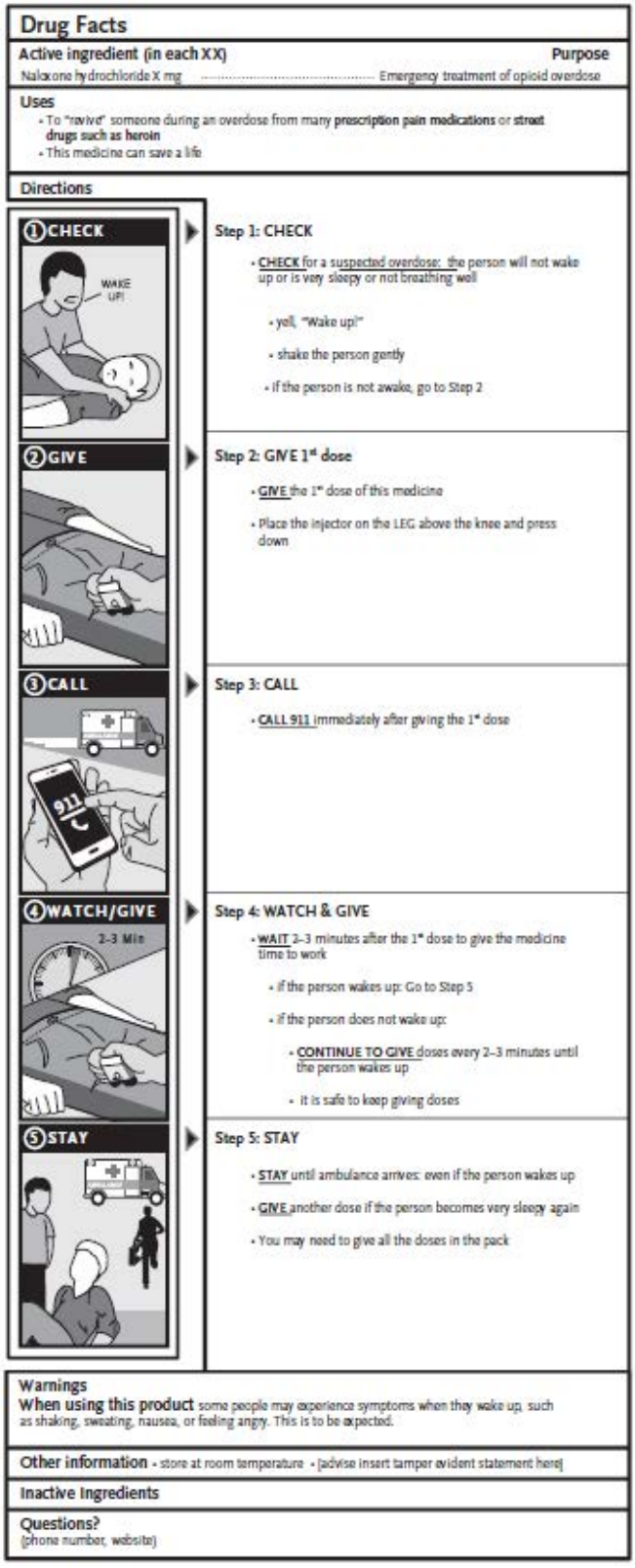
To encourage naloxone applicants to enter the nonprescription market and accelerate the development of nonprescription naloxone, FDA took an unprecedented approach to study, develop, test, and validate two versions of a model naloxone DFL. The model DFLs were developed by FDA clinicians and social scientists/communication 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 by bystanders in an emergency overdose situation. 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 2023) and were published in the *New England Journal of Medicine* (Cohen et al. 2020).

The Applicant's proposed DFL used FDA's model naloxone DFL for a nasal spray (Figure 3, column 1) as its foundation.

Figure 3. FDA Model Naloxone DFLs for Use With Either a Nasal Spray or Autoinjector (Respectively)





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 sequential tasks. In Task 1, FDA clinicians and communications experts, in consultation with outside experts in addiction treatment, developed a draft DFL. This draft DFL had simple language and adjacent pictograms. It was tested in iterative, qualitative one-on-one testing in two groups of potential consumers. One consumer group was composed of "all comers," while the remaining group was composed of participants recovering from substance abuse. Findings from Task 1 led to a revised model DFL aimed at achieving optimal comprehension.

Task 2 involved conducting a pilot LCS with consumers using the model DFL. The aim of this task was to establish the necessary sample size for a pivotal LCS and to evaluate consumer comprehension of the potential 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 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 with experience recruiting limited literacy populations in Tampa, Dallas, Los Angeles, Raleigh, Durham, and New York City.

To reflect the two consumer-friendly, approved forms of naloxone available at the time the research was designed (nasal spray and autoinjector), two model naloxone DFLs with associated pictograms for each dosage form were prepared. The DFL section related to the particular dosage form (Step 2 of the Directions) was included as a placeholder and was not tested as part of the study. The remaining content was identical for both DFL versions. The model naloxone DFL for the nasal spray is shown in (Figure 3).

In the first part of the pivotal LCS, the cognitive walkthrough method was used to allow participants to talk aloud about the sequence of action steps listed in the model naloxone DFL. Cognitive walkthroughs were included because of the unique labeling, which included a sequence of critical actions that needed to be completed in an emergency situation. This process is not typical of nonprescription drug products. The cognitive walkthrough allowed participants to describe the stepwise sequence involved in the administration of naloxone more naturally, and was intended to help the interviewer more accurately determine whether participants understood the stepwise sequence involved in the administration of naloxone. All participants were asked to (a) imagine that they were in a situation in which they had to use the product on a friend, and (b) state how they would use this drug product based on the DFL instructions for use. The interviewer then documented the steps described in the cognitive walkthrough as well as the order in which they were mentioned. This was followed by a more standard label comprehension interview that mainly included open-ended questions describing third-party scenarios.

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

Table 7. Primary and Secondary Endpoints

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

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

Because "Step 3: Call 911 immediately" was determined by FDA to be the most important endpoint, it was assessed at a higher prespecified LB threshold (90%) than the other endpoints. "Step 3: Call 911 immediately" was recognized as the most important among the instructions for use because, in an overdose situation, the bystander's role is to get the unconscious individual into the hands of a healthcare professional (HCP) as quickly as possible, while delivering life-saving treatment. Naloxone alone may not be enough for a successful resuscitation.

The remaining four steps and the composite of Steps 1 to 3 were assessed at an a priori LB threshold of 85%, given their slightly lower level of importance when compared with the "Step 3: Call 911 immediately" instruction. Two other labeled statements concerning the use of naloxone and signs of overdose were also determined to be important enough to be primary endpoints, but not as important as previously mentioned instructions (e.g., "Product use: Treatment of opioid overdose"; see Table 7). Therefore, the LB thresholds for these primary endpoints were set at 80%.

Demographics of the Label Comprehension Population

A total of 720 participants were enrolled in the study, with 710 of these participants completing the interview portion of the study. Table 8 shows that, among the sample (N=710), 51% of the

participants were males and 49% of the participants were females. The mean age of the participants was 37.6 years (SD=±15.6), with nearly 20% of the sample younger than 18 years old. Participants predominantly identified as White (65.4%) and Black or African American (31.1%), with about 10% of the sample self-identified as "Hispanic or Latino" (Table 8). A total of 473 participants (66.6%) were determined to have normal literacy, while the remaining 237 participants (33.4%) were determined to have limited literacy.

Table 8. Demographics of the Study Population

Variable	Overall n (%)	Normal Literacy n (%)	Limited Literacy n (%)
REALM category			
Limited literacy	237 (33.4%)	0 (0.0%)	237 (100.0%)
Normal literacy	473 (66.6%)	473 (100.0%)	0 (0.0%)
User segment			
Opioid user/associate (Groups 1, 2)	430 (60.6%)	294 (62.2%)	136 (57.4%)
Adolescent all comers (Group 3)	140 (19.7%)	88 (18.6%)	52 (21.9%)
Adult all comers (Group 4)	140 (19.7%)	91 (19.2%)	49 (20.7%)
Highest education level attained			
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%)

Variable	Overall n (%)	Normal Literacy n (%)	Limited Literacy n (%)
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%)
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's table.
Abbreviations: n, number of subjects with a given variable; REALM, Rapid Estimate of Adult Literacy in Medicine; SD, standard deviation

Primary Endpoints: Results

Table 9 shows that among the eight primary endpoints, six met or exceeded the prespecified target threshold. The primary endpoints that did not meet the targeted thresholds were the "Step 3: Call 911 immediately" and "Composite of steps 1-3" endpoints. Analyses of the interview transcripts revealed that most participants who answered incorrectly on the former endpoint referred to the "Call 911" statement but did not specify that they would "call 911 immediately" after the first dose. Common reasons for incorrect responses included (but were not limited to) statements that participants would call 911 only if the person (a) did or (b) did not wake up, or (c) after waiting to see if the dose worked. Twenty-five participants did not mention calling 911. Participants with poorer comprehension of this endpoint were more likely to have limited literacy, have lower educational attainment, be Black, or be unfamiliar with naloxone.

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

Table 9. Primary Endpoints: Results

Primary Endpoint	Target LB Threshold	Overall N=710 Correct Response % (LB, UB)	Normal Literacy N=473 Correct Response % (LB, UB)	Limited Literacy N=237 Correct Response % (LB, UB)
Step 1: Check for a suspected overdose	85	95.8 (94.0, 97.1)	97.9 (96.1, 99.0)	91.6 (87.3, 94.8)
Step 2: Give the first dose of this medicine	85	98.2 (96. 9, 99.0)	99.8 (98.8, 99.9)	94.9 (91.3, 97.4)
Step 3: Call 911 immediately	90	90.3 (87.9, 92.4)	94.7 (92.3, 96.6)	81.4 (75.9, 86.2)
Composite of steps 1-3	85	81.1 (78.0, 83.9)	87.9 (84.7, 90.7)	67.5 (61.2, 73.4)

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 4: Repeated doses every few minutes until the person is fully awake or until emergency personnel arrive	85	93.8 (91.8, 95.5)	97.3 (95.4, 98.5)	86.9 (81.9, 90.9)
Step 5: Stay with the person until the emergency personnel arrive	85	91.1 (88.8, 93.1)	95.1 (92.8, 96.9)	83.1 (77.7, 87.7)
Use for treatment of opioid overdose	80	96.5 (94.9, 97.7)	98.1 (96.4, 99.1)	93.2 (89.3, 96.1)
Signs of overdose	80	94.5 (92.6, 96.1)	98.1 (96.4, 99.1)	87.3 (82.4, 91.3)

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

Secondary Endpoints: Results

There were five secondary endpoints. The results shown in Table 10 indicate that the associated DFL messages were well understood by most participants, with point estimates exceeding 80% for nearly all secondary endpoints, with the exception of the composite score for getting all five steps correct (74.6% PE). Of those participants who did not state all five steps correctly, more than half stated four of the five steps correctly (53.9%), and more than three-quarters 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 10. Secondary Endpoints: Result

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

Source: FDA review

Qualitative Endpoints: Results

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

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

Conclusion

FDA's model naloxone DFLs and their associated pictograms generally tested well for comprehension across groups in a pivotal LCS. There are some important distinctions between FDA's model naloxone DFL and the Applicant's proposed DFL (see Figure 4 for the Applicant's proposed DFL and carton). These distinctions include the addition of product-specific pictograms and instructions for administering RiVive (Steps 2 and 4) and changes to the "Call 911" instructions (Step 3). In this instance, the potential impact and implications of any differences between the Applicant's proposed DFL and FDA's model naloxone DFL are more appropriately evaluated in a well-designed HFVS. For more information on the Applicant's HFVS, refer to Sections 7.7.3 and 7.7.4 as well as the detailed review by Division of Medication Error Prevention and Analysis II (DMEPA II) dated May 2, 2023 (DARRTS Reference ID: 5166245).

Figure 4. Applicant's Proposed Nonprescription RiVive (Naloxone HCl) Nasal Spray DFL and

Source: NDA 217722 submitted October 28, 2022
Abbreviations: DFL, drug facts label; HCl, hydrogen chloride

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No original nonclinical data were submitted to support the safety of this NDA. The Applicant is relying upon NDA 016636 (Narcan [naloxone hydrochloride 0.4 mg/mL] injection) to support

nonclinical safety. Additional nonclinical summary information was written by Dr. Chibueze Ihunnah and is 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 the approved injectable Narcan prescribing information (PI) may be attributable to the reversal of the effects of the opioid. The PI 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 the neonate, opioid withdrawal may also include convulsions, excessive crying, and hyperactive reflexes.

The injectable Narcan PI 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 mostly in patients who 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

RiVive is not approved in the U.S. market or in any foreign market; therefore, no postmarketing experience is available for RiVive specifically. However, other IN naloxone products are approved in the U.S. market. The analyses of postmarketing safety data for these other IN naloxone products are presented in Section 7.6.2.

7.4. FDA Approach to the Safety Review

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

Naloxone has a wide safety margin and a well-established safety profile with over 50 years of postmarketing experience. The proposed product demonstrated naloxone exposure that was comparable to that of the approved injectable Narcan (NDA 016636). A single dose of RiVive demonstrated systemic exposures that are roughly similar to 1.3 mg IM naloxone, which falls within the approved initial dosing range for Narcan (0.4 mg to 2 mg). The systemic safety of the proposed product is supported by its PK data as compared to those of injectable Narcan.

The proposed product’s formulation and route of administration are different compared to the reference injectable Narcan product. Thus, clinical safety data generated in the two clinical

pharmacology studies are necessary to support these differences of the proposed product. These data will be reviewed in Section 7.6.1.

To explore the potential safety concerns of RiVive in the nonprescription space, the Applicant conducted a review of 7 years of domestic and foreign postmarketing safety data as well as literature published over a 7-year period, paying special attention to potential safety issues that may arise during nonprescription use. The primary value of these evaluations was to identify unexpected or serious events not previously recognized for naloxone products in general and, to the extent possible, identify AEs and their relative frequencies specific to the proposed product. This evaluation utilized several postmarket safety databases including:

- FAERS
- WHO Vigibase
- AAPCC NPDS

The Applicant gave special attention to several relevant safety topics of interest, including product ineffectiveness, rebound opioid toxicity, use errors, drug hypersensitivity, and acute opioid withdrawal syndrome.

Additionally, 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 IN naloxone cases occurring in the community setting). This independent review of FAERS and the published literature gave 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 are provided in Section 7.6.2.3; 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 RiVive, the Applicant developed nonprescription packaging and labeling. 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. A high-level summary of the HFVS's limitations and findings are provided in Section 7.7.4. For a full review of the HFVS qualitative data, please refer to the DMEPA II review dated May 2, 2023 (DARRTS Reference ID: 5166245).

7.5. Adequacy of the Clinical Safety Database

Ninety-six healthy subjects were exposed to the proposed IN naloxone product in the Applicant's clinical studies. Of these 96 subjects, 93 subjects received two doses, and three subjects received one dose. All the studies used the intend-to-market formulation (HRT001 naloxone HCl nasal spray 3 mg). Considering naloxone's well-established safety profile, wide safety margin, and extensive postmarketing experience, the clinical safety database is adequate.

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

7.6. Safety Results

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether it was considered drug-related or not. Therefore, an AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with use of a drug product. In the clinical studies, AEs were attributed to the most recent treatment received prior to the AE. Treatment-emergent adverse events (TEAEs) were defined as any AEs not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. 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.

7.6.1. Clinical Safety Results

The safety evaluation was adequate for the product's proposed indication, dosage regimen, duration, and patient population.

7.6.1.1. Study HRT001-PK01

Overview and Objectives

HRT001-PK01 was a phase 1, randomized, open-label, two-sequence, four-period, single-dose crossover study conducted to assess the relative BA and PK profile of HRT001 IN naloxone 3 mg (T, test product) relative to 0.4 mg IM naloxone administered in the deltoid (R, reference product) in 38 healthy male and female adult subjects. The study took place in Austin, TX, between August 2020 and January 2021.

The primary objective was to assess the relative BA of HRT001 naloxone HCl nasal spray 3 mg compared with 0.4 mg of IM naloxone in healthy adult subjects. The secondary objectives of the study were to assess the relative BA of HRT001 in the first 10 minutes postdose and to assess its safety and tolerability.

Methodology

The study consisted of a screening period, four check-ins, four treatment periods, and an end-of-study visit. Treatment periods were separated by a washout period of at least 4 days following each dose. Thirty-eight subjects were randomized into one of two treatment sequence groups: Sequence 1 (TRTR) or Sequence 2 (RTRT). The sequence was randomly assigned, and each subject received both study treatments twice. This study took place during the coronavirus disease 2019 (COVID-19) pandemic, and all subjects wore KN95 masks provided by the site for at least 24 hours before treatment administration and during the postadministration period, except for dose administrations and meals.

Safety and tolerability assessments included monitoring of AEs; 12-lead electrocardiograms; vital sign measurements (blood pressure, pulse rate, respiratory rate, temperature); clinical laboratory tests (hematology, biochemistry, urinalysis); and examination of the IN mucosa at check-in, 15 minutes, 30 minutes, 1 hour, and 4 hours after IN administration; and at end of

study. Subjects receiving IM injections did not undergo a nasal mucosal exam. Table 11 describes IN irritation scoring.

Table 11. Intranasal Irritation Scoring

Score	Findings
0	Normal appearing mucosa, no bleeding
1	Inflamed mucosa, no bleeding
2	Minor bleeding that stops within 1 minute
3	Minor bleeding taking 1 to 5 minutes to stop
4	Substantial bleeding for 4 to 60 minutes, does not require medical intervention
5	Ulcerated lesions, bleeding that required medical intervention

Source: eCTD Module 5.3.1.2 HRT001-PK01 Report Body, submitted September 30, 2022; Table 9-1.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

Demographics

Most subjects were White (27/38; 71.1%), followed by Black or African American (8/38; 21.1%) and Asian (3/38; 7.9%). Thirteen subjects (13/38; 34.2%) had an ethnicity of Hispanic or Latino. Similar numbers of males and females participated (18 males, 47.4%; 20 females, 52.6%). The mean age of subjects was 39.0 years, with a range of 19 to 55 years.

Safety Results

Overall, 14 subjects (14/38; 36.8%) reported 24 TEAEs. Of these 24 events, 11 AEs in five subjects (5/36; 13.9% of subjects dosed with treatment T) were considered related to treatment T, and no AEs were related to treatment R. Four TEAEs (two events of nausea and two events of vomiting) reported by one subject while receiving IN naloxone were assessed as moderate in severity, and the remaining TEAEs were assessed as mild. All TEAEs resolved by the end of the study. Table 12 below lists all drug-related AEs by treatment arm.

Table 12. Drug-Related TEAEs (Treatment T and Treatment R), HRT001-PK01

Drug-Related AEs	Treatment T	Treatment R
Dysgeusia	5	-
Nausea	4	-
Vomiting	2	-

Source: eCTD Module 5.3.1.2 HRT001-PK01 Report Body, submitted September 30, 2022; Listing 14.3.2.1.
Abbreviations: AE, adverse event; R, reference product; T, test product; TEAE, treatment-related adverse event

There were no deaths, serious adverse events (SAEs), or discontinuations due to study drug.

Three subject discontinuations occurred. One subject (Subject (b) (6)) discontinued due to a nonserious AE of symptomatic COVID-19 found by his primary physician; this subject received only one dose of treatment R and no doses of treatment T. A second subject withdrew from the study (the Applicant did not state the reason); this subject received only one dose of treatment T and no doses of treatment R. A third subject discontinued for other reasons ("subject no show"); this subject received only one dose of treatment R and no doses of treatment T. All 38 randomized subjects were included in the safety population.

No result from the subjects' vital signs, laboratory testing, electrocardiogram results, or IN mucosal examinations was reported as a TEAE, other than one positive test for SARS-CoV-2 RNA in Subject (b) (6)

Nasal irritation was evaluated using the six-point scale described above. Three subjects had a nasal irritation score of "1" (inflamed mucosa, no bleeding), and the remainder of the subjects had a nasal irritation score of "0" (normal appearing mucosa, no bleeding). The abnormal scores occurred between 15 minutes to 4 hours after administration of IN naloxone. All abnormal scores resolved by end of study. The three subjects with abnormal nasal irritation scores did not report any AEs found to be drug-related. One subject reported a mild TEAE of epistaxis the day after administration of IN naloxone, which was not considered to be treatment-related. None of these three subjects reported any nasal symptoms. The investigators did not code the abnormal examination findings as AEs in this study, in contrast to HRT001-PK02.

Overall, the risk of these relatively mild AEs is outweighed by the potentially lifesaving benefit of naloxone.

7.6.1.2. Study HRT001-PK02

HRT001-PK02 was a two-part study conducted in Toronto, Canada, from October 2021 to February 2022. Each subject participated in either Part I or Part II of the study but not both.

7.6.1.2.1. Part I

Overview and Objectives

Part I was a phase 1, randomized, open-label, single-dose, four-period, two-treatment, two-sequence, crossover replicate study conducted to assess the relative BA and PK profile of HRT001 IN naloxone 3 mg (T, test product) relative to 0.4 mg IM naloxone (R, reference product) in 36 healthy male and female adult subjects. The primary objective of Part I was to assess the comparative BA of HRT001 relative to IM naloxone 0.4 mg. The secondary objectives of Part I were to assess the relative BA in the first 10 minutes postdose and to evaluate the safety and tolerability of the study treatments.

Methodology

In Part I, the test product (treatment T) consisted of one actuation of HRT001 naloxone nasal spray 3 mg into the right nostril, and the reference product (treatment R) consisted of one injection of 0.4 mg/mL naloxone HCl solution into either the right or left dorsogluteal muscle. Part I consisted of a screening period, four check-ins, four treatment periods, and an end-of-study visit. Treatment periods were separated by a washout period of at least 7 days following each dose. Subjects were randomized into one of two treatment sequence groups: Sequence 1 (TRTR) or Sequence 2 (RTRT).

Safety and tolerability assessments were the same as those in HRT001-PK01, except olfactory testing was performed in HRT001-PK02. A four-item version of the U.S. National Health and Nutrition Examination Survey (NHANES) Pocket Smell Test was conducted at each check-in and at end of study (only for treatment T in Part I). The investigator was contacted if more than two incorrect answers were identified. All AEs were coded using MedDRA version 24.1.

It is noted that the NHANES eight-item smell test was designed as a screening test, and a result of six, seven, or eight correct answers is considered normal (Rawal et al. 2015). The eight-item test is based on a 40-item test from the University of Pennsylvania (Rawal et al. 2015). The Applicant used the NHANES eight-item test but reduced the number of items to four and considered a result of three or four correct answers to be normal. The four-item test is not validated.

Demographics

Most subjects were White (17/36; 47.2%); nine subjects were Asian (9/36; 25.0%); nine were Black or African American (9/36; 25.0%); one subject was White and Asian (1/36; 2.8%). Nine subjects had an ethnicity of Hispanic or Latino (9/36/25.0%). Twenty-two subjects were female (22/36; 61.1%); 14 subjects were male (14/36; 38.9%). Subjects' ages ranged from 23 to 55 years.

Results

Thirty-six subjects enrolled in Part I of the study; all were included in the safety analyses. Overall, 28 subjects (28/36; 77.8% of subjects dosed) reported 52 TEAEs. A total of 48 TEAEs were assessed as drug-related, including 46 TEAEs in 27 subjects (27/36; 75.0%) after treatment T and two AEs in two subjects (2/36; 5.6%) after treatment R.

Of the 52 AEs in both treatment arms, 50 TEAEs were assessed as mild, and two TEAEs were assessed as moderate (two reports of nasal mucosal disorder after treatment T). The drug-related AE with the highest incidence was nasal mucosal disorder, with 20 events affecting 19 subjects (19/36; 52.8% of subjects). Most of these were mild in severity (18/20; 90%). Dysgeusia was the second most frequently noted AE in the treatment T subgroup (n=15). The Applicant reported all other TEAEs occurred less frequently, were of mild severity, and resolved by end of study without intervention. Table 13 below shows all drug-related TEAEs by treatment arm.

Table 13. Drug-Related Treatment-Emergent Adverse Events (Treatment T and Treatment R), HRT001-PK02 Part I

Drug-Related Treatment-Emergent Adverse Events	Treatment T Number of Reports	Treatment R Number of Reports
Nasal mucosal disorder[1]	20	-
Dysgeusia	15	1
Nasal congestion	4	1
Mucosal hemorrhage[2]	2	-
Epistaxis	1	-
Eyelid pruritus	1	-
Neutrophil count decreased‡	1	-
Upper airway cough syndrome	1	-
White blood cell count decreased[3]	1	-
Total	46	2

Source: Adapted from eCTD Module 5.3.1.2 HRT001-PK02 Report Body, submitted September 30, 2022; Table 12-9.
[1] The reported terms erythema and mild erythema were coded as the preferred term nasal mucosal disorder.
[2] The reported terms tiny blood spot and 2-3 blood spots were coded as the preferred term mucosal hemorrhage.
[3] Lab abnormality resolved on repeat testing without intervention.
Abbreviations: R, reference product; T, test product

There were no deaths, SAEs, or discontinuations due to the study drug in HRT001-PK02 Part I. One subject was withdrawn from the study after Period 3 due to dry cough and sore throat, which were assessed as unrelated to the study drug.

In comparing the results from the first olfactory test to the results at end of study, most subjects (91.7%; 33/36) had either no change (n=30) or an increase in the number of correctly identified items (n=3). Three subjects had a decrease in the number of correctly identified items; each subject correctly identified one fewer item at end of study than at the first check-in. Given the use of an unvalidated four-item Pocket Smell Test for this assessment, the clinical significance of these findings is unclear.

Reviewer comment: Compared to the reference treatment arm, the number of drug-related AEs involving IN naloxone appears high, but several listed AEs (nasal mucosal disorder, nasal congestion, and mucosal hemorrhage, which collectively account for 26/46 drug-related TEAEs) were related to examination findings that were not associated with any subject-reported nasal symptoms. The most frequently occurring TEAE was "nasal mucosal disorder" (n=20), which was coded when an examiner found "mild erythema" or "erythema" on the nasal cavity examination. All erythema events were mild in severity, except two that were classified as moderate. Investigators coded "nasal congestion" (n=4) when examinations showed swelling of the nasal mucosa. Examination findings triggered all four reports of nasal congestion in the treatment T subgroup. There was no documentation of subject-reported complaints of nasal congestion in this subgroup. Investigators coded "mucosal hemorrhage" (n=2) when examiners found "tiny blood spot" and "2-3 blood spots" during the nasal mucosal exam. The blood spots resolved by 60 minutes postdose and were not associated with any subject-reported nasal complaints. Subjects did not experience nasal symptoms related to exam findings of nasal mucosal erythema, swelling, and blood spots, so these observations are of uncertain clinical significance.

7.6.1.2.2. Part II

Overview and Objectives

Part II was a phase 1, randomized, open-label, single-dose, two-period, two-treatment, two-sequence, crossover relative BA study with a primary objective of assessing the impact of prolonged mask-wearing on the absorption of HRT001 IN naloxone 3 mg in 24 healthy male and female adult subjects. The secondary objective of Part II was to evaluate the safety and tolerability of the study treatments.

Methodology

Treatment A consisted of one actuation of HRT001 in subjects who wore a KN95 mask for at least 24 hours prior to drug administration and up to the last time of the last PK blood sample of the period. Masks were removed for dosing and meals. Treatment B consisted of one actuation of HRT001 into the right nostril without mask-wearing in the prior 24 hours and until the last PK blood sample was drawn. Part II consisted of a screening period, two check-ins, two treatment periods, and an end-of-study visit. Treatment periods were separated by a washout period of at least 7 days following each dose. Subjects were randomly assigned to one treatment sequence (Sequence AB or Sequence BA).

Safety and tolerability assessments were conducted in the same way as in Part I.

Demographics

Ten subjects were White (10/24; 41.7%); nine were Black or African American (9/24; 37.5%); five subjects were Asian (5/24; 20.8%). Seven subjects had an ethnicity of Hispanic or Latino (7/24/29.2%). Thirteen subjects were female (13/24; 54.2%); 11 subjects were male (11/24; 45.8%). Subjects' ages ranged from 22 to 55.

Results

Twenty-four subjects enrolled in Part II; all 24 subjects were included in the safety analyses. Overall, 20 subjects (20/24; 83.3%) reported 59 TEAEs. Of these, 58 TEAEs were assessed as related to the study drug, including 16 subjects who received treatment A (16/22; 72.7%) reporting 29 drug-related AEs, and 16 subjects who received treatment B (16/24; 66.7%) reporting 29 drug-related AEs. The Applicant reported all AEs were mild in severity and were resolved prior to end of study without intervention.

The most common drug-related AEs in subjects receiving IN naloxone were nasal mucosal disorder, nasal congestion, and dysgeusia. All AEs in Part II were assessed as mild. There were no significant differences comparing safety outcomes between subjects wearing a mask (treatment A) and subjects not wearing a mask (treatment B). Table 14 below shows all drug-related TEAEs by treatment arm.

Table 14. Drug-Related Treatment-Emergent Adverse Events (Treatment A and Treatment B), HRT001-PK02 Part II

Drug-Related Treatment-Emergent Adverse Event	Treatment A Number of Reports	Treatment B Number of Reports
Nasal mucosal disorder[1]	16	16
Nasal congestion	10	9
Dysgeusia	2	2
Nasal discomfort	1	0
Oropharyngeal pain	0	1
Paresthesia[2]	0	1
Total	29	29

Source: Adapted from eCTD Module 5.3.1.2 HRT001-PK02 Report Body, submitted September 30, 2022; Table 12-10.
[1] The reported terms erythema and mild erythema were coded as the preferred term nasal mucosal disorder.
[2] The reported term tingling sensation of the right nostril was coded as the preferred term paresthesia.

No deaths, SAEs, or discontinuations due to the study drug occurred in HRT001-PK02 Part II. Three subject discontinuations occurred in Part II; none were assessed as related to the study drug.

In comparing the results from the first olfactory test to the results at end of study, most subjects (83.3%; 20/24) had either no change (n=16) or an increase in the number of correctly identified items (n=4). Four subjects had a decrease in the number of correctly identified items; three subjects correctly identified one fewer item at end of study compared to the first check-in, and one subject correctly identified two fewer items at end of study compared to the first check-in. Given the use of an unvalidated four-item Pocket Smell Test for this assessment, the clinical significance of these findings is unclear.

Reviewer comment: Similar to the coding method used in Part I of this study, nasal mucosal disorder was coded when an examiner found "mild erythema" or "erythema" on the nasal cavity examination, and nasal congestion events included instances in which the examiner found swelling of the nasal mucosa. Of the 20 subjects with erythema or swelling on nasal mucosal exam, only two subjects reported any nasal symptoms. One subject who had erythema and swelling on exam also reported nasal congestion. Another subject who had erythema on exam with treatment A and treatment B also reported slight burning in the nostril with treatment A and tingling sensation in the nostril with treatment B.

7.6.2. Adverse Events Identified in Postmarket Experiences

All postmarketing safety databases are susceptible to inherent limitations, including but not limited to: underreporting, a lack of reporting standards, incomplete reporting, duplication, reporter bias, and the presence of potential confounding factors within a case that preclude a causal assessment. Many factors can influence whether or not an event will be reported, such as the amount of time a product has been marketed and publicity about an event. Additionally, there is no way to know the true denominator of patient exposure or the true number of cases for any AE. Therefore, pharmacovigilance safety data cannot be used to calculate the incidence of an AE or medication error in the U.S. population. Although these issues limit our ability to draw definitive conclusions based on the postmarketing experience, analyses of this information can provide some useful insights as to potential unexpected or serious events not previously recognized for products similar to RiVive and, to the extent possible, evaluate AEs that might represent issues for the proposed product and could inform its labeling.

7.6.2.1. Drug Utilization

To estimate potential patient exposure to naloxone in the United States, FDA conducted an independent analysis of naloxone distribution and utilization. This section provides a summary of the findings. For a full review, please refer to the OSE Consult Review dated February 27, 2023 (DARRTS Reference ID: 5131876).

From 2016 to 2021, manufacturer sales and dispensed prescriptions of all naloxone formulations increased dramatically. Manufacturers sold approximately (b) (4) units of naloxone in 2016, which more than doubled to nearly (b) (4) units in 2021. These increases were largely driven by increases in sales of nasal spray formulations, which increased from approximately (b) (4) units in 2016 to (b) (4) units in 2021 (Figure 5).

Figure 5. Nationally Estimated Number of Naloxone Units (Vials, Syringes, Nasal Sprays) Sold From Manufacturers to U.S. Channels of Distribution, Stratified by Product Formulation, Annually 2016 to 2021

Source: IQVIA National Sales Perspective™, Time period 2016 to 2021, data extracted Jan 2023.
(b) (4)

These data do not include direct sales or donations from manufacturers to groups such as harm reduction organizations.

There was a similar shift towards nasal sprays in the dispensed prescription analysis. The number of naloxone prescriptions dispensed from U.S. outpatient retail, mail-order, and long-term care pharmacies increased from approximately (b) (4) prescriptions in 2016 to (b) (4) prescriptions in 2021, mainly due to an increase in the nasal formulation. The proportion of nasal formulations dispensed among the total naloxone prescriptions increased from approximately (b) (4)% in 2016 to (b) (4)% in 2021.

It is noted that naloxone products are often distributed outside the traditional pharmacy supply chain to reach those without health insurance, those who are using illicit substances who may be reluctant to seek medical care, and family and friends of opioid users. These distribution channels may include products donated or sold directly to groups such as harm reduction programs, prisons, and other entities. The units distributed outside the traditional pharmaceutical distribution supply chain are not captured in estimates obtained from proprietary databases available to FDA. It is also important to note that sales distribution and dispensed prescription data do not provide a direct estimate of use (what is administered to individuals). Naloxone is obtained as a preventative measure to reverse opioid overdose and is stored until it may be needed in an emergency situation. If the product is not used before it expires, it may end up not being used at all.

7.6.2.2. Summary of Applicant's Postmarketing Safety Analysis

For this NDA, the Applicant provided an analysis of domestic and foreign postmarketing safety data for IN as well as nonnasal naloxone using FAERS, WHO Vigibase, and the NPDS. The Applicant notes that case narratives were not available from FAERS or WHO Vigibase. The

medical dictionary used for the FAERS and WHO searches was MedDRA version 24.1. NPDS utilizes its own dictionary of clinical effects. The Applicant conducted a literature search using PubMed to look for U.S. reports of AEs. To highlight data most relevant for consideration of an IN product, this review focuses on AEs that occurred more frequently with an IN route of administration than with nonnasal routes of administration. All analyses covered a 7-year period from January 1, 2015, through December 31, 2021.

7.6.2.2.1. FDA Adverse Event Reporting System

General Findings

The Applicant identified a total of 1,468 cases in which naloxone was used by any route of administration. These cases reported a total of 6,573 AEs. When age was known, most of the cases were reported in patients 18 years of age or older (739/1,468, 50.3% of all cases; not reported 678/1,468, 46.2%). When gender was known, more cases were reported in females (655/1,468, 44.6% of all cases) than in males (594/1,468, 40.5% of all cases; not reported 219/1,468, 14.9%). When route of administration was known, IN naloxone was reported in 288 cases, and nonnasal naloxone (includes any other nonmissing route) was reported in 321 cases. Most cases (859/1,468; 58.5%) did not report a route of administration.

Analysis of Serious Cases

Of the cases with an IN route of administration, 29.5% were assessed as serious. In comparison, 92.7% of cases with a nonnasal route of administration were serious. Fatal cases comprised 6.3% of all cases reporting an IN route of administration (18 cases) and 10.9% of all cases reporting a nonnasal route of administration (35 cases). The remaining 174 fatal cases did not report the route of administration.

Reviewer comment: Opioid overdose is a serious condition, which, without treatment, leads to death. Thus, the frequency of serious outcomes, including death, noted among reported cases is not unexpected. Although route of administration information was not reported for a majority of all cases as well as for most fatal cases, the available data suggest there was a lower frequency of both serious outcomes and death in cases with IN administration as compared to cases with nonnasal administration.

Analysis by Age

Among cases with an IN route of administration, when age information was reported, only one pediatric case was reported; all others (119/120; 99.2%) were reported in patients 18 years of age or older. In the single pediatric case, which was nonserious, the preferred terms (PTs) vomiting and anger were reported in an adolescent patient. A total of 14 cases in patients ≥65 years were reported; four of these cases were serious (28.6%).

In comparison, for nonnasal routes, age was reported in 204 of 321 cases (63.6%). Of the cases reporting an age, 22 were reported in patients <18 years; all pediatric cases were serious. There were 46 cases in patients ≥65 years, of which 45 (97.8%) were serious.

Reviewer comment: It is reassuring that since the approval of IN naloxone in 2015, there has been only one pediatric case reporting nonserious AEs and no cases reported in children <2

years. The percentage of serious cases in patients ≥65 years was notably lower with the IN route (29.6%) than with nonnasal routes (97.8%), which is supportive of the proposed IN product.

Analysis of AEs With Higher Frequency in Intranasal Route of Administration Compared to Nonnasal Route of Administration

Out of all the reported PTs, eight PTs demonstrated a higher frequency with the IN route of administration than with the nonnasal route (see Table 15).

Table 15. FAERS PTs With Higher Frequency in Intranasal Route of Administration Compared to Nonnasal Route of Administration

	Intranasal Route N=288		Nonnasal Route N=327		Percent Difference Between IN Route and Nonnasal Route
Adverse Event Preferred Term	n	%	n	%	%
Unintentional use for unapproved indication	42	14.6%	0	0%	14.6%
Vomiting	43	14.9%	8	2.4%	12.5%
Feeling abnormal	25	8.7%	0	0%	8.7%
Drug withdrawal syndrome	39	13.5%	22	6.7%	6.8%
Anger	20	6.9%	1	0.3%	6.6%
Withdrawal syndrome	21	7.3%	5	1.5%	5.8%
Malaise	17	5.9%	6	1.8%	4.1%
Nausea	12	4.2%	7	2.1%	2.1%

Source: Adapted from eCTD Module 5.3.5.3 Report 1: Reports of Postmarketing Experience and Integrated Analysis of FAERS and VigiBase, submitted September 30, 2022; Table 13.
Abbreviations: FAERS, FDA Adverse Event Reporting System; IN, intranasal; PT, preferred term

Reviewer comment: Overall, compared to the millions of nasal spray units distributed by manufacturers during the reporting period, the total number of cases reporting an IN route of administration (288) was small. A slight difference in the number of reports for a specific PT can cause the difference in percentage to appear relatively large when, in fact, the absolute number of cases is low.

Although the AEs listed in the table above were reported more frequently with IN naloxone than in nonnasal naloxone, most of them are known AEs of naloxone or are nonspecific (such as feeling abnormal or malaise), and they are generally not serious. Use for wrong indication is discussed in Section 7.6.2.3.4. The potential benefit of reversing opioid overdose outweighs the risks of these adverse effects.

Adverse Events of Special Interest

The Applicant reviewed five safety topics of interest:

Product Ineffective

For the IN route of administration, there were 27 cases (27/288; 9.4%) with product ineffective events defined using four PTs associated with limited efficacy (absence of immediate treatment response, drug ineffective, therapeutic product effect delayed, and treatment failure). Of these 27 cases, the most frequently reported PT was drug ineffective (22/288, 7.6%). One product ineffective case was fatal.

In comparison, for nonnasal routes of administration, these four PTs representing product ineffective events were reported in 29 cases (29/327; 8.9%). Of these cases, the PT drug ineffective was also the most frequently reported (26/327; 8.0%). Four product ineffective cases were fatal.

Reviewer comment: Product ineffective events were reported with similar frequency when comparing cases associated with IN versus nonnasal routes of administration. There are several potential reasons for naloxone to be reported ineffective, including but not limited to: the patient needed earlier administration of naloxone; the patient needed a repeat dose of naloxone; the patient had a nonopioid overdose; the patient had an opioid overdose caused by partial opioid agonists or mixed agonist/antagonists; medication use errors; and product issues. A lack of case details precludes assessment of causality. Additionally, considering the relatively small numbers of cases accrued and small numerical differences noted between IN and nonnasal routes of administration, these findings are generally reassuring that product ineffectiveness appears to occur infrequently. Considering the large amount of naloxone distributed during the reporting period, these reported AEs represent a very small proportion of the expected exposed population.

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. Re-emergence of opioid overdose symptoms is possible because the duration of action of some opioids exceeds that of naloxone; thus, repeat doses of naloxone are sometimes required.

The Applicant attempted to evaluate rebound opioid toxicity for IN naloxone formulations by analyzing cases that reported at least one PT associated with the condition. The search included 42 PTs that the Applicant selected to try to establish that a case represented rebound opioid toxicity. The full list is provided in Section 17 (Table 43) and includes terms such as overdose and respiratory failure. A total of 123 cases (123/288; 42.7% of cases with an IN route of administration) were identified.

Reviewer comment: Many of the PTs selected by the Applicant to conduct its search could have been associated with either the original opioid overdose or rebound opioid toxicity. For example, the PT overdose (41/288; 14.2% of cases with an IN route of administration) could be attributed to the original overdose or to recurrent opioid toxicity. Similarly, respiratory failure (6/288; 2.1%) could occur in either scenario. The limitations of the databases and lack of access to case narratives preclude clinical confirmation or meaningful conclusions regarding rebound opioid toxicity. Rebound toxicity is not an adverse effect directly associated with naloxone use, and when it occurs, it suggests that more naloxone is needed. Having another naloxone product available as a nonprescription product may increase availability and accessibility to allow for repeated administration. RiVive's labeling addresses the potential need for repeat doses and emphasizes the importance of "Call 911" as a key step in the instructions for use. The mean serum half-life value for RiVive was 1.36 hours. If RiVive is used according to the label, calling 911 will activate emergency medical services early and will help mitigate issues that may arise from rebound opioid toxicity.

Use Errors

To evaluate the topic of use errors for IN naloxone formulations, the Applicant searched for the 35 PTs listed in Section 17, Table 44. There were 73 cases with errors associated with the use of an IN route of administration (73/288; 25.3%). Within the category of errors, user error (66/73; 90.4%) was the most frequently reported error subtype. The most frequently reported PT was unintentional use for unapproved indication (42/288; 14.6% of all cases with an IN route of administration), followed by wrong technique in product usage process (4/288; 1.4%).

Reviewer comment: The frequency of unintentional use for unapproved indication may reflect the relative ease of using a nasal spray. Nasal spray products are used for common conditions such as allergic rhinitis and nasal congestion. A person may mistake a naloxone nasal spray for a different nasal product. Additionally, because the causes of overdose symptoms are not easily distinguishable for laypeople, a caregiver or bystander may administer naloxone to someone who is not breathing but actually has a nonopioid overdose or a different problem altogether. The limitations of the databases and the lack of access to case narratives preclude clinical confirmation or meaningful conclusions. Nonetheless, as a nonprescription product, RiVive's labeling underwent label comprehension testing and human factors testing, which should minimize potential use error. See relevant sections of the review for these analyses.

Drug Allergy and Hypersensitivity

To evaluate this topic, the Applicant used the standardized MedDRA query for hypersensitivity. Among the cases with an IN route of administration, there were a total of 16 cases (16/288; 5.6%), including 13 serious cases and 3 nonserious cases. Among the cases with a nonnasal route of administration, there were a total of 38 cases (38/321; 11.8%), including 36 serious cases and 2 nonserious cases.

Reviewer comment: The lack of case details preclude confirmation whether AEs were related to naloxone use or other concomitant drugs. However, drug allergy is a known potential AE that can arise from use of naloxone. Nonetheless, since the label advises calling 911, any hypersensitivity reactions can be monitored and addressed by medical professionals. Additionally, because 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.

Opioid Withdrawal

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 for 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.

To analyze the topic of opioid withdrawal, the Applicant created a list of potential opioid withdrawal symptoms by mapping terms from the 2020 version of injectable Narcan's PI to MedDRA 24.1 and adding other relevant terms from the standardized MedDRA query for drug withdrawal. The 40 PTs included in the query are listed in Section 17, Table 45.

Reviewer comment: The search likely overestimated the number of withdrawal cases because it included PTs that overlap with AEs associated with opioid overdose (e.g., cardiac arrest, coma, death, hypotension, pulmonary edema, and seizure). Some PTs represent minor or nonspecific symptoms, such as abdominal pain, crying, hypertension, myalgia, nausea, rhinitis, sneezing, vomiting, and yawning.

Across all routes of administration, there were 642 cases of potential opioid withdrawal (642/1,468; 43.7%). A total of 149 cases were associated with IN naloxone (149/288; 51.7%), including 52 serious cases (52/288; 18.1%) and 97 nonserious cases. A total of 165 cases were associated with nonnasal routes of naloxone administration (165/321; 51.4% of all cases with a nonnasal route of administration), including 160 serious cases (160/321; 49.8%) and 5 nonserious cases. The remaining majority of cases was associated with an unknown route of administration.

Reviewer comment: The frequency of potential opioid withdrawal was relatively high for both IN and nonnasal routes of administration; however, a smaller subset reported serious outcomes related to IN naloxone use than with nonnasal naloxone.

Reports of opioid withdrawal are not unexpected. Naloxone is indicated for the emergency treatment of opioid overdose. It can be expected that a proportion of overdoses will occur in those who are physically dependent on opioids. The injectable Narcan PI notes that naloxone may precipitate opioid withdrawal. On balance, because naloxone treats opioid overdose and may save the life of the patient, the benefits of naloxone outweigh the risk of precipitated withdrawal.

7.6.2.2.2. WHO VigiBase

The 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 reactions 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.

General Findings

The Applicant identified 1,957 cases in which naloxone was a suspected product during the 7-year reporting period. These cases reported a total of 5,075 AEs. When gender and age information were known, most cases were reported in patients ≥18 years (1,442/1,957, 73.7%; not reported 457/1,957, 23.4%), and more cases were reported in males (1,013/1,957, 51.8%; females 805/1,957, 41.1%; not reported 139/1,957, 7.1%). When route of administration was known, IN naloxone was reported in 258 cases, and nonnasal naloxone (includes any other nonmissing route) was reported in 405 cases. Most cases (1,319/1,957; 67.4%) did not report a route of administration.

Analysis of Serious Cases

Of the 258 cases with an IN route of administration, 26.4% (68/258) were assessed as serious. In comparison, of the 405 cases with a nonnasal route of administration, 46.4% (188/405) were serious. Fatal cases comprised 5.8% (15/258) of all cases reporting an IN route of administration and 7.2% (29/405) of all cases reporting a nonnasal route of administration. The remaining 94 fatal cases did not report the route of administration.

Analysis by Age

Among cases in which an IN route of administration and age information were reported, all but one (104/105; 99.0%) were in patients ≥18 years. In the single exception, which had a nonserious outcome, the PTs of vomiting and anger were reported in a patient in the ≥12 to <18 years age group. In patients ≥65 years, there were a total of 13 cases, 4 of which were serious. In comparison, for nonnasal routes, age was reported in 334 of 393 cases (85.0%). Of these, 24 were reported in patients <18 years; 17 of these cases were serious. There were 90 cases in patients ≥65 years, of which 38 (42.2%) were serious.

Analysis of AEs With Higher Frequency in Intranasal Route of Administration Compared to Nonnasal Route of Administration

Out of all the reported PTs, eight PTs demonstrated a higher percentage of AEs in the IN route of administration as compared to the nonnasal route (see Table 16).

Table 16. VigiBase Preferred Terms With Higher Frequency in Intranasal Route of Administration Compared to Nonnasal Route of Administration

	Intranasal Route N=258		Nonnasal Route N=405		Difference in Percentage Between IN Route and Nonnasal Route
Adverse Event Preferred Term	**n**	**%**	**n**	**%**	**%**
Unintentional use for unapproved indication	38	14.7%	0	0%	14.7%
Feeling abnormal	22	8.5%	0	0%	8.5%
Vomiting	36	14%	23	5.7%	8.3%
Drug withdrawal syndrome	30	11.6%	15	3.7%	7.9%
Anger	20	7.8%	1	0.2%	7.6%
Overdose	34	13.2%	23	5.7%	7.5%
Withdrawal syndrome	20	7.8%	8	2%	5.8%
Malaise	15	5.8%	6	1.5%	4.3%

Source: Adapted from eCTD Module 5.3.5.3 Report 1: Reports of Postmarketing Experience and Integrated Analysis of FAERS and VigiBase, submitted September 30, 2022; Table 14.
Abbreviations: IN, intranasal

Reviewer comment: Similar AEs were noted to occur more frequently with IN routes of administration versus nonnasal routes of administration in Vigibase as in FAERS. Most AEs listed in the table are known AEs of naloxone or are nonspecific and are generally not serious.

Adverse Events of Special Interest

Product Ineffective

The Applicant used the same method as in the FAERS analysis to identify cases for the product ineffective topic and identified 23 cases (23/258; 8.9%) that were associated with IN naloxone. Of these 23 cases, the most frequently reported PT was drug ineffective (19/258; 7.4%). Because 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 why naloxone may not be effective. The frequency and PTs reported among the identified cases in Vigibase are generally consistent with findings from FAERS.

Rebound Opioid Toxicity

The Applicant attempted to evaluate Vigibase for cases of rebound opioid toxicity related to use of IN naloxone. Using the same search method as in the FAERS search on this topic, the Applicant retrieved a total of 103 cases (103/258; 39.9%). As noted previously, the limitations of the databases and the lack of access to case narratives precludes a meaningful conclusion.

Use Errors

The Applicant evaluated Vigibase for cases involving IN naloxone that reported issues related to use errors. Using the same search method previously described, the Applicant identified 69 such cases (69/258; 26.7%). User error (57/69; 82.6% of all cases reporting error) was the most frequently reported error subtype. The most frequently reported PT was unintentional use for unapproved indication (38/258; 14.7%). These findings are consistent with findings noted within FAERS.

Drug Allergy and Hypersensitivity

The Applicant evaluated Vigibase for cases involving naloxone that reported issues related to drug allergy and hypersensitivity. Using the same search method previously described, the Applicant identified 12 cases (12/258; 4.7%) involving IN naloxone, including 10 serious cases and 2 nonserious cases. 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; these findings are consistent with those noted in FAERS.

Opioid Withdrawal

The Applicant evaluated Vigibase for cases involving naloxone that reported symptoms of opioid withdrawal. Using the same search method previously described, the Applicant identified 128 such cases (128/258; 49.6%) involving IN naloxone, including 37 serious cases (37/258; 14.3%) and 91 nonserious cases. The lack of access to case narratives precludes a meaningful conclusion; however, these results are consistent with the findings from FAERS.

7.6.2.2.3. National Poison Data System

The Applicant searched for cases with single-ingredient naloxone exposure from the AAPCC NPDS. The AAPCC maintains NPDS, which houses de-identified case records of self-reported information collected from callers during exposure management and poison information calls

managed by the country's poison control centers. NPDS notes that reports of drug exposure do not necessarily represent a poisoning or overdose. Additionally, NPDS uses its own dictionary of clinical effects instead of MedDRA.

General Findings

During the 7-year reporting period, poison centers received reports of 1,093 cases that included exposure to single-ingredient naloxone by any route of administration. These cases reported a total of 2,639 clinical effects. When gender and age information were known, most patients were ≥18 years of age (981/1,093; 89.8%), and the gender distribution was about half female (531/1,093; 48.6%) and half male (488/1,093; 49.7%). Age was unknown in 3.7% of cases (40/1,093).

Of all 1,093 cases, the majority (600/1,093; 54.9%) reported naloxone exposure only with no exposure to any other drug products. The remainder of cases involved more than one drug product. AE data were captured at the case level, so if a given case involved more than one drug product, AEs could not be tied to a specific drug product, including naloxone. Thus, within NPDS, the Applicant analyzed the clinical effects specifically related to single-ingredient naloxone exposure by examining cases with naloxone exposure only.

Analysis by Route of Administration

Of the 600 cases with naloxone exposure only, the three most frequently reported routes of exposure were inhalation/IN (273/600; 45.5%), parenteral (177/600; 29.5%), and ingestion (86/600; 14.3%). Routes of administration were not mutually exclusive; a case could have more than one route of administration.

Reviewer comment: The NPDS data combine the inhalation and IN routes of administration into a single category. FDA has approved IN naloxone products, but no approved inhaled naloxone products exist. Thus, use of naloxone via inhalation would be considered off-label. We cannot determine the specific route of administration for cases reported from the data.

Analysis of Fatal Cases

There were no fatalities among cases reporting naloxone exposure only.

Analysis by Age

Among naloxone exposure only cases with an inhalation/IN route of administration, when age information was reported, a total of 15 pediatric cases (15/273; 5.5%) were reported. The majority (248/273; 90.8%) of cases involved patients ≥18 years. Age was unknown in 10 inhalation/IN cases.

Among the 15 pediatric cases, 5 cases reported a total of 6 clinical effects. Ten cases did not report any clinical effects. Clinical effects reported among cases involving children <2 years of age included one case each of CNS depression (mild) and CNS depression (moderate). Clinical effects reported among cases involving children ≥2 to <12 years of age included one case each of nausea and chest pain (including noncardiac). In the ≥12 to ≤18 years age group, one case reported administration of 16 mg of naloxone in a patient who had clinical effects of nausea and abdominal pain.

Reviewer comment: Overall, the small number of pediatric cases and reports of only six clinical effects are reassuring. The clinical effects noted appear to be largely consistent with the known effects of naloxone or the underlying condition of opioid overdose.

Analysis of AEs With Higher Frequency in Intranasal Route of Administration Compared to Nonnasal Route of Administration

Overall, many cases (110/273) with naloxone exposure only and an inhalation/IN route of exposure did not include a reported clinical effect.

Across all reported clinical effects in cases of naloxone exposure only, 22 clinical effects demonstrated a higher frequency for the inhalation/IN route than for nonnasal routes. The five clinical effects with the largest differences in frequency are listed in Table 17.

Table 17. Clinical Effects With a Higher Frequency of Reporting for Inhalation/Intranasal Versus Nonnasal Routes of Administration in Cases of Naloxone Exposure Only, Five Clinical Effects With Largest Difference

	Inhalation/ Intranasal N=273		Nonnasal N=310		Percentage Difference Between Inhalation/IN Route and Nonnasal Route
Clinical Effect	n	%	n	%	%
Vomiting	36	13.2%	19	6.1%	7.1%
Diarrhea	25	9.2%	9	2.9%	6.3%
Pain (not dermal, GI, ocular)	17	6.2%	4	1.3%	4.9%
Other–Miscellaneous	39	14.3%	37	11.9%	2.4%
Other–Neurological	16	5.9%	11	3.5%	2.3%

Source: Adapted from eCTD Module 5.3.5.3 Report 2: American Association of Poison Control Centers/National Poison Data System (AAPCC/NPDS), submitted September 30, 2022; Table 17; and eCTD Module 5.3.5.3 NPDS Post-text Tables and Listings, submitted September 30, 2022; Table 1.8.1.
Abbreviations: GI, gastrointestinal; IN, intranasal

Reviewer comment: Vomiting and diarrhea, the two clinical effects with the largest differences in frequency between inhalation/IN and nonnasal routes, are consistent with the known effects of naloxone. The other clinical effects in the above table are nonspecific.

7.6.2.2.4. Literature Review

The Applicant conducted a review of the published medical literature relevant to the clinical safety of single-ingredient naloxone with a publication date from January 1, 2015, through December 31, 2021. The Applicant identified 121 publications for inclusion that consisted of 55 clinical studies, 55 case reports/series, and 11 review articles. The publications cited by the Applicant generally identified known AEs of naloxone, AEs expected with an opioid overdose, AEs associated with the use of nasal sprays, and AEs that are more likely related to underlying medical conditions rather than the use of naloxone. Overall, the literature review did not identify any new safety issues that would impact the proposed product's safety profile or nonprescription availability.

7.6.2.3. FDA's Postmarketing Safety Analysis

OSE was consulted to evaluate AEs associated with IN naloxone use in the community setting using FAERS and the published literature for the period between January 1, 2016, and November 17, 2022. Attention was directed to safety topics of interest including naloxone-induced precipitated withdrawal, limited efficacy, and device use errors/medication errors. This section provides a summary of the findings; for a full review, please refer to the OSE Consult Review dated February 27, 2023 (DARRTS Reference ID: 5131876). The search was conducted utilizing MedDRA version 25.1.

7.6.2.3.1. Intranasal Naloxone in Community Setting

A total of 318 cases reporting IN naloxone use in the community setting were identified. Analysis of the cases indicated that those administering the naloxone were either the general public (untrained laypeople) (157/318; 49.4%), trained laypeople (non-HCP with formal training in naloxone dosing, basic life support, or other skills) (27/318; 8.5%), HCPs (13/318; 4.1%), or unknown (119/318; 37.4%). A total of 79.2% of cases reported the reason for IN naloxone use was emergency treatment of known or suspected opioid overdose, 18.2% reported accidental use, and 2.5% reported a nonindicated condition. Cases were assessed for number of doses administered, and most reported the use of only one or two doses, that is, up to 8 mg.

Serious outcomes were noted in 81 cases (81/318; 25.5%). When age information was available, most serious cases (21/81; 25.9%) occurred among patients 18 to 65 years of age, no serious cases occurred in children less than 18 years of age, and three cases (3/81; 3.7%) occurred in those greater than 65 years of age. Age was not reported in 57 serious cases (57/81; 70.4%).

Table 18 shows the most frequently reported PTs (with an n≥5) among serious cases involving IN naloxone use in the community setting.

Table 18. Most Frequently Reported Preferred Terms (n≥5) Among Serious Cases Involving IN Naloxone Use in the Community Setting

MedDRA PT	Number of FAERS Reports[1]
Drug ineffective	18
Drug withdrawal syndrome	12
Death	10
Vomiting	10
Withdrawal syndrome	9
Loss of consciousness	7
Seizure	7
Feeling abnormal	6
Headache	5
Hyperhidrosis	5
Unintentional use for unapproved indication	5

Source: FDA Review
[1] A case may contain more than one PT
Abbreviations: FAERS, FDA Adverse Event Reporting System; IN, intranasal; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term

The most frequently reported PTs from serious cases appear to be related to naloxone-induced precipitated withdrawal (e.g., drug withdrawal syndrome, vomiting, withdrawal syndrome, hyperhidrosis, seizure; further discussed in Section 7.6.2.3.2) and limited efficacy (i.e., drug

ineffective; further discussed in Section 7.6.2.3.3). Other common PTs (e.g., death, loss of consciousness, feeling abnormal, headache) are likely related to the underlying opioid overdose and/or are nonspecific. Note that not all cases with a serious outcome of death (n=15) in this case series reported a PT of death (n=10). Additionally, note that the PT unintentional use for unapproved indication is most often associated with accidental use of a product for the wrong indication (further discussed in Section 7.6.2.3.4).

7.6.2.3.2. Naloxone-Induced Precipitated Withdrawal

In order to assess opiate withdrawal in the cases selected, the Clinical Opiate Withdrawal Scale (COWS) was used to evaluate cases of reported naloxone-induced precipitated withdrawal. COWS is a tool for clinicians to diagnose and manage opioid withdrawal (Wesson and Ling 2003). It was developed in the late 1990s, initially as a guide for buprenorphine treatment. It is most frequently used for differentiating the presence versus absence of withdrawal as well as identifying clinically significant withdrawal. Since the early 2000s, it has become more widely used as a clinical tool due to ease of administration and consistency between evaluators. 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.

A case met the definition of naloxone-induced precipitated withdrawal if either an HCP 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; the actual score may have been higher.

A total of 180 cases (180/318; 56.6%) were identified reporting withdrawal or symptoms consistent with withdrawal. No deaths were reported, and 35 withdrawal cases (35/180; 19.4%) reported a serious outcome. Gastrointestinal upset, anxiety/irritability, and sweating were the most commonly scored items on the COWS scale. Overall, a majority of cases (159/180; 88.3%) had a COWS score of less than 5. Twenty-one cases (21/180; 11.7%) were identified with a COWS score ≥5, and no case scored more than 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 in the community IN naloxone case series. Both pulmonary edema cases were reported by a non-HCP as withdrawal but did not report any COWS symptoms. Of the eight cases reporting the PT seizure, five reported naloxone-induced withdrawal, and three did not. Most cases lacked details surrounding the seizure that occurred (e.g., seizure not witnessed or no further information provided in the narrative other than that the patient experienced a seizure). Several cases are confounded by other medications involved in the overdose that could cause seizures (e.g., methamphetamine or unknown medications), or potential misidentification of withdrawal-related restlessness as a seizure.

Cases reported in FAERS reflect the known AE of naloxone-induced precipitated withdrawal, which is included in the prescription naloxone injection PI under Warnings 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 suggest that although symptoms of naloxone-induced precipitated withdrawal were reported with some frequency (56.6% of IN naloxone 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 a patient, the benefits of naloxone outweigh the risk of precipitated withdrawal.

7.6.2.3.3. Limited Efficacy

Multiple factors contribute to the effectiveness of IN naloxone, including severity of overdose, involvement of other substances, inadequate dose of naloxone, involvement of superpotent opioids, time between overdose and naloxone administration, and administration technique. Naloxone needs to be administered as promptly as possible after overdose to prevent mortality and morbidity.

The 318 cases describing IN naloxone 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. 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 not knowing the amount of time that 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 because cases often provided limited information, precluding a meaningful assessment. Information about the time elapsed between when an overdose occurred and when naloxone was administered was often unreported. Additionally, 75% of cases did not report the specific opioid intended to be reversed (e.g., partial agonists) or if other substances were involved in the overdose, both of which could affect the efficacy of naloxone. Thus, it was not possible to fully ascertain the reasons for limited efficacy in most cases.

As noted above, many factors contribute to whether naloxone use will be effective. Delayed or unknown timing of naloxone administration after an overdose event was the most common factor appearing in at least 25% of limited efficacy cases. Cases reporting that “nothing came out” may have been related to use errors or product issues, but limited information precluded a meaningful assessment. It is noted that all emergency use devices are assessed for robustness at approval and manufacturers are expected to comply with current good manufacturing practices regulations at all times. See Section 9.1 for a discussion about device reliability. Overall, there was a small number of cases identified with limited efficacy because “nothing came out.” Additionally, it is noted that the nonprescription labeling for RiVive 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.

In the setting of an opioid epidemic that includes increasing exposures to fentanyl and its analogs, an issue for consideration is whether RiVive will effectively reverse overdoses caused by superpotent opioids. To be approved, novel naloxone products, including RiVive, must demonstrate the same or greater systemic absorption of naloxone compared to an approved naloxone product, particularly in the early critical period after drug administration. As discussed in Section 6, RiVive has met the approval standard by demonstrating a systemic exposure that is approximately the same as that of 1.3 mg of IM naloxone, which falls within the approved initial dosing range for injectable Narcan. RiVive's dose is also bracketed by the doses of two approved naloxone nasal spray products, Narcan 2 mg (NDA 208411, S-001) and Narcan 4 mg (NDA 208411). Further supporting RiVive's 3-mg dose, FDA recently made a preliminary assessment that no clinically meaningful differences exist between currently approved prescription and potential nonprescription naloxone nasal sprays up to 4 mg (87 FR 68703, November 16, 2022).

The literature on naloxone doses effective against superpotent opioids is difficult to analyze because of the necessarily retrospective nature of such reports and frequently encountered confounding factors. Such factors include but are not limited to: recall bias associated with retrospective studies, frequent lack of detail about strength and doses of naloxone used during a reversal, variations in route of administration including off-label IN use of injectable forms of naloxone, and variable amounts of time awaited between naloxone doses. Nonetheless, two publications appear to support the effectiveness of current naloxone doses against overdoses involving fentanyl. Carpenter et al. conducted a retrospective chart review of patients who had received naloxone through an emergency medical services agency in Atlanta from January 1, 2017, to June 15, 2018, and found no significant difference among the naloxone doses required to treat opioid overdose patients with evidence of exposure to fentanyl, opiates, or both (Carpenter et al. 2020). The authors concluded that the "findings refute the notion that high potency synthetic opioids like illicitly manufactured fentanyl require increased doses of naloxone to successfully treat an overdose." Bell et al. reviewed data from the Allegheny County Medical Examiner's Office on drugs that contributed to overdose deaths between 2013 and 2016 (Bell et al. 2019). During the same period, the authors interviewed people who received naloxone kits (each kit included two single-dose 1 mL vials containing 0.4 mg naloxone, two IM syringes, and an instruction card) from a community-based program. These participants administered naloxone in response to 1,072 overdoses. The authors found that although illicitly manufactured fentanyl increasingly contributed to drug overdose deaths (3.5% of fatal opioid-involved overdoses in 2013 and 68.7% in 2016), the average dose of naloxone administered had not changed significantly, with two or fewer doses reversing 89.3% (201/225) of overdoses in 2013 and 92.8% (414/446) of overdoses in 2016.

Although it is expected to reverse opioid overdoses emergently, including those involving potent opioids, RiVive will ultimately serve as a bridge to medical care. The RiVive DFL instructs users to call 911 immediately after administering the first dose. While awaiting emergency medical services, users are instructed to give additional doses until the person wakes up. RiVive will be packaged with two single-dose devices, which is expected to allow continued emergency treatment until an ambulance arrives as well as mitigate the concern for potential rebound opioid toxicity from opioids with half-lives longer than that of naloxone, such as fentanyl. The DFL further instructs users to "stay until ambulance arrives: even if the person wakes up," again

emphasizing the need to transfer care to emergency medical services, which can provide additional treatment, including subsequent naloxone doses, as needed.

7.6.2.3.4. Device Use Errors and Other Medication Errors

A separate FAERS search was conducted for device use errors and medication errors related to IN naloxone use. The National Coordinating Council for Medication Error Reporting and Prevention Taxonomy of Medication Errors was used to describe the medication error and contributing factors. 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 related to IN naloxone were identified in the FAERS search. All nine cases were reported as nonserious, and five of these nine cases did not report a contributing factor to the error. The cases described wrong administration technique related to device use errors, including:

- Not waiting 2 to 3 minutes between doses (n=3)
- Spraying medication into the air instead of patient's nostril and thus, wasting a dose (n=3)
- 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 IN naloxone occurred during an emergency when the person was not breathing or appeared not to be breathing. 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, the patients recovered. None of the six emergency situation cases reported whether the Instructions for Use/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 about 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 the cap and spray in a nostril, and they questioned if there were additional steps in between. It is noted that neither of the currently approved naloxone nasal spray devices (i.e., Narcan nasal spray [NNS] or Kloxxado) has a "cap" nor did they have a cap previously at the time of 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, those cases reported nonserious outcomes. Additionally, with the exception of one case, the remaining cases were unclear 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 2 to 3 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, a missed dose appears to be a more significant safety risk from the device use error perspective. As such, postmarket data appear to support packaging of two devices together in one carton as a single sales unit to maximize the likelihood that a dose is available when needed.

Additional Medication Errors

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

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

Wrong Indication

The wrong indication cases reported patients or caregivers mistakenly administering IN naloxone due to lack of knowledge regarding what naloxone is used for and thinking it is used for indications other than what is 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 IN naloxone 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 the patient could not understand what the product was for. Other cases did not report whether patients attempted to read and comprehend the indication for IN naloxone. However, several cases reported that patients saw "nasal spray" on the box. One case reported administration of NNS instead of Imitrex. It is noted that there is a currently marketed Imitrex product that uses the same nasal device configuration as prescription NNS; thus, the similarity between the Imitrex inhaler device and the NNS device appears to be a contributing factor for confusion.

Of the 58 cases that reported use for the wrong indication, three cases reported a serious outcome, including one death. Of the three cases reporting a serious outcome, one fatal case reported that the patient used IN naloxone 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 a result, it is difficult to assess whether IN naloxone is related to the patient's death. The two other cases reported "other" serious outcomes in patients taking opioids. One patient had been taking an unspecified opiate drug and the other had been taking morphine and oxycodone when they accidentally used IN naloxone to relieve allergy symptoms and congestion, respectively. Both patients reported withdrawal symptoms (COWS scores of 4 and 5, respectively).

Although prescription IN naloxone products state the indication on the carton labeling and instructions for use, it is unclear whether patients read the carton labeling. Additionally, in some cases, even though IN naloxone was prescribed by a doctor and filled by a pharmacy, the patients may not have realized why they were prescribed the medication. For the nonprescription product, patients or caregivers will actively select the product off the shelf. The LCS conducted for FDA's model naloxone DFL supported that general consumers were able to understand that the product's use is "to revive someone during an overdose from many prescription pain medications or street drugs such as heroin." The name and the indication of the proposed product will be prominently stated on the labeling to ensure lay users are able to see the information.

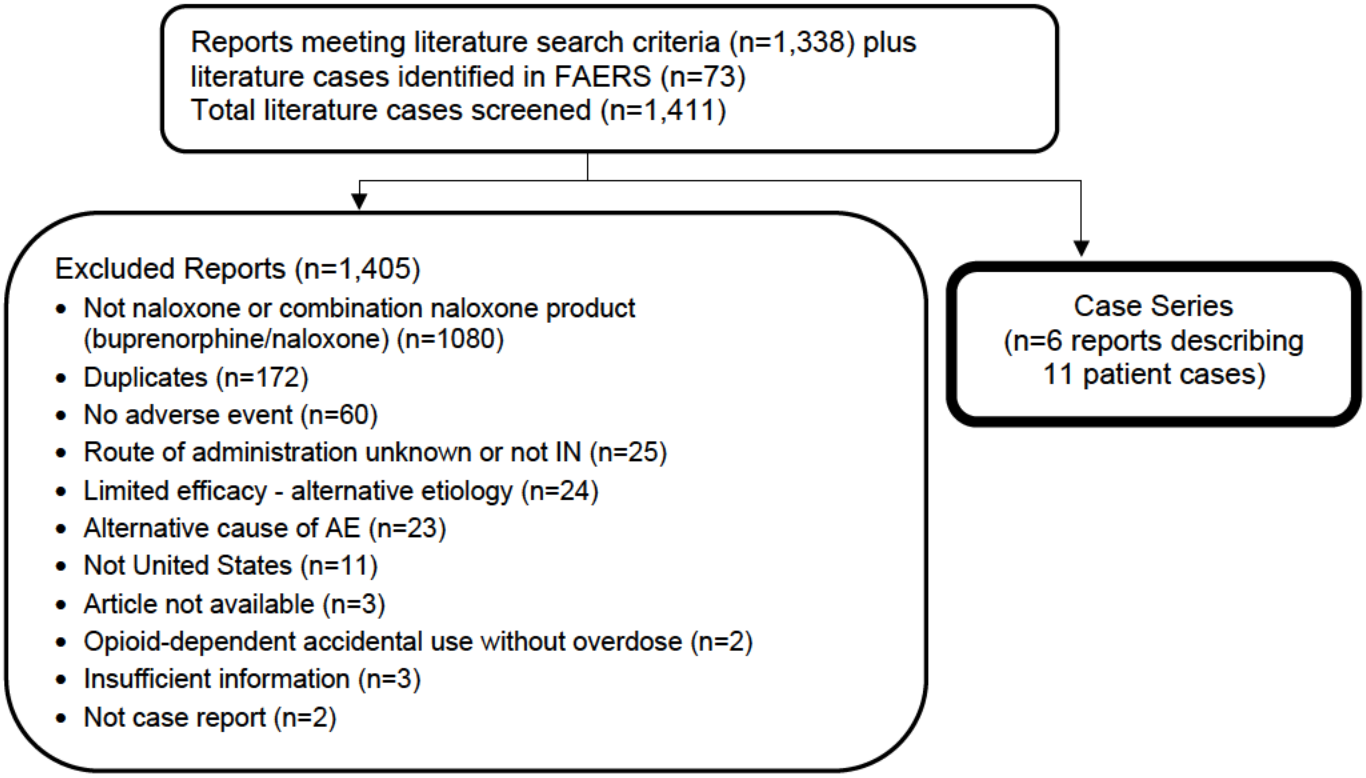
Accidental Wrong Storage

Four cases were identified related to accidental wrong storage of the product in freezing temperatures or temperatures over 104°F (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 naloxone users reported administering the product, and all four cases were considered nonserious. Nonetheless, it is recommended that the storage information on the DFL and labeling is prominently displayed to ensure visibility. Additionally, storage information should be added in other locations other than the carton (such as on the blister labeling) to help increase the chance of consumers noticing this information and to mitigate against potential errors related to storage.

7.6.2.3.5. Literature Review

FDA's review of the published literature focused on cases and case series that described use of IN naloxone with safety outcomes, as well as reviews that summarized issues related to use of IN naloxone in the community. Specifically, for the case reports reviewed by FDA, the same case selection criteria were applied to literature cases of IN naloxone as those applied to the review of FAERS reports as described in Figure 6.

Figure 6. Literature Case Selection for Intranasal Naloxone Analysis



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

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

Two cases described naloxone-induced precipitated withdrawal. One case described a patient who was given six doses of naloxone in rapid succession by an untrained bystander; the recipient experienced severe and prolonged agitation (Brenner et al. 2021). Another case described a patient with an initial COWS score of 12 after receiving one dose of IN naloxone, but the withdrawal symptoms were mitigated by a dose of buprenorphine from emergency medical services, which reduced her COWS score to 4 (Carroll et al. 2021). These cases may highlight a need to educate consumers about the symptoms of naloxone-induced precipitated withdrawal, which is captured in the proposed DFL for RiVive as a warning to expect symptoms such as shaking, sweating, nausea, or anger, as well as to reinforce the need to call 911.

Two cases described limited efficacy, requiring a higher-than-typical naloxone dose. The cases described two overdose victims with a history of heroin use who most likely also had intoxication with carfentanil, a very high-potency opioid (Bardsley 2019). These cases are instructive in that if high-potency opioids are suspected, then repeat doses of naloxone may be

required. This possibility is captured in the proposed DFL for RiVive, which advises that a dose of naloxone should be administered first, followed by calling 911 and, if the person does not wake up, continuing to give doses every 2 to 3 minutes until the person wakes up. Complicating this general advice is the possibility of an alternative unrecognized cause of somnolence that would not respond to opioid antagonism. This underscores the importance of rapidly activating emergency medical services for further evaluation and management.

7.7. Key Safety Review Issues

7.7.1. Clinical Safety of the Proposed Product

Background

RiVive's formulation and route of administration are different compared to the reference Narcan injection product (NDA 016636); thus, clinical safety data are necessary to support these differences. Safety data generated in the two clinical pharmacology studies included routine clinical safety assessments as well as local assessments of the nasal cavity.

Assessment

Safety and tolerability assessments were conducted for both PK studies (HRT001-PK01 and HRT001-PK02), including assessments of local tolerability by examination of the IN mucosa before and after treatment. Olfactory testing was also performed in HRT001-PK02.

Safety Results

A total of 98 subjects were enrolled across both PK studies, with 96 of these subjects receiving at least one dose of the to-be-marketed formulation for RiVive. Overall, a total of 52 subjects reported 115 TEAEs that were assessed as drug-related after treatment with RiVive. Table 19 lists all drug-related TEAEs. Of the 115 TEAEs, 109 (109/115; 94.8%) were assessed as mild in severity. The remaining six TEAEs were assessed as moderate in severity (including two events each of nausea, vomiting, and nasal mucosal disorder). The Applicant reported all AEs resolved prior to end of study without intervention.

Table 19. Pooled Drug-Related Treatment-Emergent Adverse Events, HRT001-PK01 and HRT001-PK02

Drug-Related Treatment-Emergent Adverse Event	Number of Reports
Nasal mucosal disorder[1]	52
Dysgeusia	24
Nasal congestion	23
Nausea	4
Mucosal hemorrhage[2]	2
Vomiting	2
Nasal discomfort	1
Epistaxis	1
Eyelid pruritus	1
Neutrophil count decreased[3]	1
Oropharyngeal pain	1
Paresthesia[4]	1
Upper airway cough syndrome	1

Drug-Related Treatment-Emergent Adverse Event	Number of Reports
White blood cell count decreased[3]	1
Total	115

Source: FDA Review
[1] Nasal exam findings of erythema and mild erythema were coded as the PT nasal mucosal disorder.
[2] Nasal exam findings of a "tiny blood spot" and "2-3 blood spots" were coded as the PT mucosal hemorrhage.
[3] Lab abnormality resolved on repeat testing without intervention.
[4] The reported term tingling sensation of the right nostril was coded as the PT paresthesia.

There were no deaths or SAEs reported. Seven subjects discontinued from the studies, but none of the discontinuations were due to study drug.

Olfactory testing, using a modified four-item version of the validated NHANES eight-item odor identification test, was performed in HRT001-PK02. Among all 60 subjects participating in study HRT001-PK02, 53 subjects experienced either no change or an increase in the number of correct smells identified from baseline to end of study (46 subjects demonstrated no change and 7 subjects demonstrated an increase in the number of correctly identified items). Of the seven remaining subjects, six identified one fewer item at end of study compared to the first check-in, and one subject identified two fewer items at end of study compared to the first check-in. These findings are of unclear clinical significance.

Conclusion

Clinical safety data showed most AEs were mild and self-limited. Most AEs were related to abnormal nasal exam findings such as erythema and nasal mucosal swelling, but most subjects with these findings did not report any associated symptoms. Olfactory testing showed most subjects had no change in or an improvement in their scores; the clinical significance of a one- or two-point change in score in a small fraction of subjects using an unvalidated olfactory test is unclear. Overall, the risk of these relatively mild AEs is outweighed by the potentially lifesaving benefit of naloxone.

7.7.2. Adverse Events From Postmarketing Safety Data Associated With Use of Approved Intranasal Naloxone Products

Background

RiVive is not approved in the U.S. market or in any foreign market; therefore, no postmarketing experience is available for RiVive specifically. However, other IN naloxone products are approved in the United States and worldwide. The Applicant provided an analysis of domestic and foreign postmarketing safety data for IN naloxone with special attention to potential safety issues that may arise during nonprescription use. FDA also conducted an independent evaluation of FAERS for AEs associated with naloxone, particularly IN naloxone use in the community setting.

Assessment

The Applicant assessed postmarketing safety data using FAERS, WHO Vigibase, the NPDS, and the published literature. FDA's review of the Applicant's assessment of the postmarketing safety data revealed no new safety signals of concern. The Applicant's findings showed that there were

relatively fewer cases reporting AEs associated with IN as compared to nonnasal routes of naloxone administration. Serious and fatal outcomes associated with IN naloxone were less frequent than with nonnasal routes of naloxone administration. Pediatric and geriatric cases were reported infrequently in IN naloxone cases. The most commonly reported AEs were similar across all databases and included unintentional use for unapproved indication, vomiting, feeling abnormal, and drug withdrawal syndrome.

FDA's review of FAERS also provided reassuring findings. It is noted that in about half the cases, naloxone was administered by the general public (i.e., untrained laypeople), and the majority of the outcomes reported were nonserious. Most cases described using one to two doses, up to a cumulative 8-mg dose of naloxone, and reported a reason for use as an emergency treatment of known or suspected opioid overdose, reflecting appropriate use of IN naloxone by the general public. Overall, the FAERS analysis did not identify any new safety issues related to AEs from IN naloxone use in community settings. The most frequently reported AEs were consistent with those known for naloxone. The review included evaluations of additional safety topics including naloxone-induced precipitated withdrawal, risk of limited efficacy, and use errors (including device use errors as well as errors related to use for the wrong indication and wrong storage). The risk of these AEs, especially considering the small volume of reports identified among a large potential patient exposure during this time period, do not appear to outweigh the potential benefit of increased community availability.

Conclusion

Postmarketing safety data for IN naloxone do not reveal any new safety issues. Consumers generally administered IN naloxone for the correct indication, and most cases had nonserious outcomes. Relatively few cases were identified reporting serious naloxone-induced precipitated withdrawal or limited efficacy. The highest risk device use error was spraying naloxone outside of the nostril, which may be mitigated by packaging two devices in one carton. Wrong indication and storage errors were identified and may be mitigated by clear and prominent labeling.

7.7.3. Limitations of Human Factors Validation Study Methodology

7.7.3.1. Pediatric Users Less Than 12 Years of Age Were Not Included in the HFVS

Background

The Applicant proposed to include the pediatric user group's age range of 12 to 17 years in the HFVS protocol submitted to the Agency for review. 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). Upon further consideration, we now generally recommend that HFVSs include pediatric participants 10 to 17 years old.

Assessment

The Applicant states that the intended users of the product include adolescents and adults. The HFVS included pediatric participants 12 to 17 years old.

Conclusion

Because pediatric users less than 12 years old were not tested, the data collected may not be generalized to the untested age range of the adolescent user group.

7.7.3.2. Moderators Employed Use of Leading Language

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).

Assessment

Participants in the HFVS were instructed by the study moderator to “follow the instructions on the box” prior to demonstrating use of the product in a simulated overdose scenario.

Conclusion

Leading language may have introduced a bias towards positive performance, which is taken into consideration when interpreting the HFVS results.

7.7.4. Qualitative Human Factors Validation Study Findings

We reviewed the qualitative dataset provided by the Applicant including all use errors (UE), close calls (CC), and use difficulties (UD). We also reviewed all subjective feedback from participants collected by the Applicant (if available), the Applicant’s root cause analysis for each error (when provided), and the Applicant’s proposed mitigations. A high-level summary of the results is provided in Table 20.

Table 20. High-Level Summary of HFVS Results for Steps 2, 3, and 4

Steps	Number of Use Errors (UE)	Number of Close Calls (CC)	Number of Use Difficulties (UD)
Step 2: Give a dose of this medicine	9 UE: • General population (n=3) • Adolescent (n=4) • Opioid user/Associate (n=2)	5 CC: • General population (n=2) • Adolescent (n=2) • Opioid user/Associate (n=1)	2 UD: • Adolescent (n=1) • Opioid user/Associate (n=1)
Step 3: Call 911	11 UE: • General population (n=2) • Adolescent (n=7) • Opioid user/Associate (n=2)	17 CC: • General population (n=8) • Adolescent (n=3) • Opioid user/Associate (n=6)	0 UD
Step 4: Watch & give	42 UE: • General population (n=15) • Adolescent (n=15) • Opioid user/Associate (n=12)	2 CC: • General population (n=1) • Adolescent (n=1)	4 UD: • General population (n=1) • Adolescent (n=2) • Opioid user/Associate (n=1)

Source: FDA Review
60 participants in the following user groups:
General Population: Adult general population (all comers), age 18 or older (n=20)
Adolescent: Adolescent, ages 12-17 (n=20)
Opioid User/Associates: Adult opioid users or adult opioid user associates, age 18 or older (n=20)
Abbreviations: CC, close calls; n, number of subjects; UD, use difficulties; UE, use errors

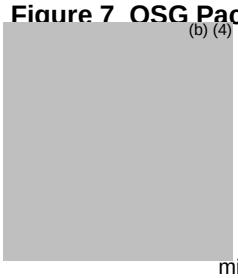
Use-related events occurred in the study that may be attributed to the user interface (labeling and packaging design). Relevant findings and our recommendations for these use-related events are detailed below.

7.7.4.1. Users Did Not Identify the QSG or Had Difficulty Using It

Background

Some participants did not notice the QSG packaged inside the blister or did not identify that the folded paper contained instructions because the folded QSG that is visible through the blister packaging contains a repeated pattern of a caduceus (see Figure 7), whereas the side that includes the statement, “Unfold for User Instructions” is printed on the side of the QSG that is not visible through the blister packaging (See Figure 8). Additionally, some participants had difficulty opening the QSG or tore the QSG while opening.

Figure 7. QSG Packaged Inside the Blister



mission
Abbreviations: QSG, Quick Start Guide

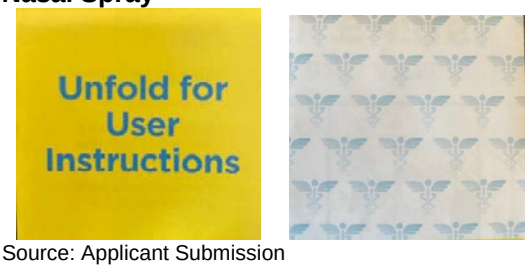
Assessment

We anticipate that some users will carry the blister and not the complete carton. Therefore, if the carton DFL is unavailable at the time of administration, UEs of this nature may result in delayed administration of naloxone if users have difficulty locating or accessing instructions.

To address the errors, the Applicant considered printing the statement "Unfold for User Instructions" in large blue font against a yellow background (see Figure 8) on both sides of the QSG, and explored a less sticky glue to allow the QSG to be unfolded more easily.

We agree and recommend the Applicant implement the mitigations they are currently considering. Additionally, for the purposes of the proposed nonprescription product and to align with the DFL, the "Quick Start Guide" labeling should be retitled as "DIRECTIONS" to help users quickly identify that this piece of paper contains identical instructions to the DFL Directions.

Figure 8. Yellow Background Versus Repeated Pattern of a Caduceus of the Tested Quick Start Guide; Repeated Pattern of Caduceus Side is Seen by Users Through the Clear Blister Behind the Nasal Spray



Source: Applicant Submission

Conclusion

We recommend retitling the "Quick Start Guide" labeling as "DIRECTIONS" to help users quickly identify that this piece of paper contains identical instructions to the DFL Directions. We also recommend printing the statement "Unfold for Directions" to help users quickly identify that this piece of paper contains identical instructions to the DFL Directions.

We recommend printing the statement "Unfold for Directions" on both sides of the folded QSG in large blue font against a yellow background. We recommend using less sticky glue to keep the QSG folded.

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

Background

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

Assessment

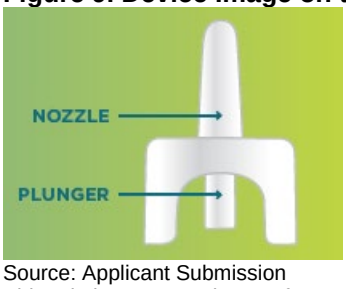
Some participants held the nasal spray device in a manner inconsistent with the DFL (i.e., thumb not on plunger and a finger not on each side of the nostril). One participant's incorrect hold of the device may have contributed to the plunger being difficult to push initially; however, the participant adjusted their hold of the nasal spray device and was successful in administering a dose.

The user interface depicts the correct hand and finger position on the nasal spray device in the Step 2 pictogram and Step 4 pictogram; however, the device image on the carton labeling presents an additional opportunity to communicate correct hand and finger orientation and hold on the nasal spray.

Conclusion

We recommend that the device image on the top "fifth" panel be revised to show an image of a hand holding the device (see Figure 9). This image should show correct hand and finger positioning on the device. Due to space constraints on the top "fifth" panel, we recognize that this may require relocating the graphic image. We recommend relocating the graphic image to the principal display panel. Add the same image to the top right corner of the QSG. Incorrect hold of the device may have contributed to a use error in the HFVS.

Figure 9. Device Image on the Top "Fifth" Panel of the Carton Tested in the HFVS



Source: Applicant Submission
Abbreviations: HFVS, human factors validation study

7.7.4.3. Users Administered Spray Into the Mouth or Did Not Press the Plunger to Release the Spray

Background

Some participants experienced a UE, UD, or CC in Step 2 ("Insert nozzle into one nostril and press plunger firmly") because they put the device into the manikin's mouth or did not press the plunger.

Assessment

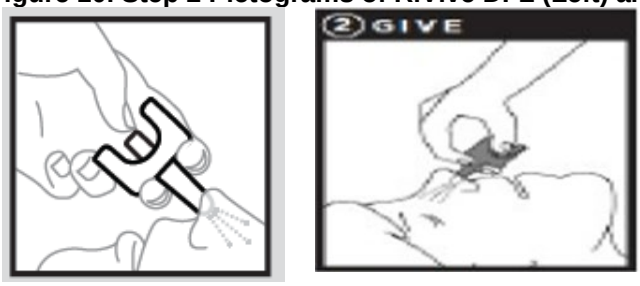
One participant did not see that the device was a nasal spray and expected to find this information on the label, and one participant thought the Step 2 pictogram depicted administration into the mouth. Additionally, one other participant did not think the Step 2 pictogram depicted the plunger being pressed.

Conclusion

We recommend that the following mitigations to minimize the observed errors:

- Adding the statement "For nose only" to the principal display panel of the carton labeling, blister labeling, and container label.
- Revising the heading of Step 2 Directions to state "Give 1st dose in the nose" instead of "Give a dose of this medicine."
- Revising the pictogram in Step 2 of the DFL and QSG to show the plunger being pressed, similar to FDA's model naloxone DFL Step 2 figure evaluated in CONFER, where the thumb appears to press down on the device (see Figure 10). Incorporate the same image into Step 4's pictogram while maintaining the clock image. Make the same revisions to the QSG.

Figure 10. Step 2 Pictograms of RiVive DFL (Left) and CONFER DFL (Right)



Source (left): Applicant Submission; Source (right): 84 FR 8728 (March 11, 2019).
Abbreviations: CONFER, Comprehension for OTC Naloxone (pivotal label comprehension study); DFL, drug facts label

7.7.4.4. A User Experienced Confusion With the Statement "Do Not Delay" in Step 3

Background

One participant with limited literacy experienced a UE and misread "do not delay" in Step 3 (Call 911) as "do not dial."

Assessment

The statement "do not delay" is unnecessary in Step 3 because the instructions state to "Get medical help immediately after giving the first dose" and "Call 911 now."

Conclusion

We recommend removing the statement "do not delay" from Step 3 Directions.

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

Background

Some participants experienced a CC in Step 3 (Call 911) because they thought one dose referred to administering both nasal spray devices, which led them to administering both nasal sprays and then calling 911 during or after administering the second dose rather than calling 911 immediately after administering the first dose. Although calling 911 after administration of the first dose is ideal, we acknowledge that these participants ultimately called 911 at some point during the use scenario.

One participant experienced a UE in Step 4 (Watch & Give) when waiting 2 to 3 minutes after the first dose to give the medicine time to work because they thought one dose referred to administering both nasal spray devices, which led them to give both doses without waiting 2 to 3 minutes.

Some participants experienced a UE, CC, or UD in Step 4 (Watch & Give) when giving a second dose of medicine using a new nasal spray because they thought the nasal spray device contained more than one dose and tried to reuse the nasal spray device previously used to administer the first dose.

Assessment

The user interface can be improved to further minimize the risk of these UEs and CCs, which, if not understood, may lead to patient harm.

Conclusion

We recommend the following to mitigate the observed errors:

- Revise the statement “Each nasal spray contains one dose of medicine” to read “1 nasal spray device contains 1 dose of medicine” on the top panel of the carton and in the third bullet in Step 2 of the DFL to convey that one dose is equivalent to one device. We recommend relocating this statement to the “fifth” panel of the carton labeling. Add the statement to the blister labeling.
- Use consistent terminology (“nasal spray device” instead of “nasal spray”) across the labels and labeling, including the DFL (e.g., in Step 2 and Step 4) for consistency and to minimize confusion.
- Add the statements “Each device sprays one time only” and “Do not test nasal spray device before use” to the “fifth” panel of the carton.

DMEPA II’s review of the HFVS results for RiVive (naloxone HCl) nasal spray identified use-related issues with critical tasks; however, DMEPA II finds the residual risk can be further mitigated by additional changes to the user interface. Although DMEPA II identified issues with the HFVS methodology, the methodology issues did not preclude the review of the HFVS results. DMEPA II’s recommendations are carefully targeted to address the root causes of use errors that occurred in the HFVS and draw upon our experience with other similar marketed products. Thus, DMEPA II finds the recommendations pose a low likelihood of introducing new

risks during use of the product and can be implemented without submitting additional HFVS data for FDA's review.

Based on the totality of information submitted and taking into consideration the public health benefit of this proposed product, DMEPA II finds the potential benefit of RiVive (naloxone HCl) nasal spray to "revive" someone during an overdose from many prescription pain medications or street drugs, such as heroin, outweighs the potential residual risk of use errors.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Not applicable

8.2. Extrinsic Factors

Not applicable

8.3. Plans for Pediatric Drug Development

The Applicant is seeking approval for RiVive for the entire pediatric age range. Because RiVive represents a new dosing regimen (3-mg dose) for naloxone nasal spray products, the Applicant was required to conduct a pediatric assessment in accordance with the Pediatric Research Equity Act. As noted previously, ethical and logistical challenges preclude controlled efficacy trials evaluating naloxone for the proposed indication in all patients regardless of age. However, unlike in adults, pediatric PK studies in healthy children are also not feasible because enrolled subjects would have no prospect of direct benefit from receiving the drug, and the study involves more than minimal risk. Thus, adult PK data coupled with evidence of safe and effective use of other naloxone drug products approved for the full pediatric age range are typically used to support pediatric use of a novel naloxone product. Using this approach, FDA has approved seven new drug applications for novel naloxone drug products to date, including six products that were approved in patients of all ages.

The Applicant received the agreed initial pediatric study plan on March 26, 2021.

No new nonclinical studies or pediatric clinical studies were conducted to support pediatric use of this novel naloxone product. The proposed product contains no novel excipients, and no reformulation was needed for pediatric use. The pediatric assessment relies on the pivotal relative BA study conducted among healthy adults and FDA's precedent of approving other naloxone nasal spray products for use down to birth that deliver naloxone with the (b) (4) nasal spray device. These other IN naloxone products all deliver the same IN volume per actuation (0.1 mL) and contain 2, 4, and 8 milligrams of naloxone, which the Applicant notes brackets the proposed 3-mg dose for RiVive. The lack of postmarketing SAEs in the pediatric population associated with other IN naloxone products, including the higher-dose 4- and 8-mg products, is also supportive of the safety for RiVive.

The Applicant submitted pediatric safety data available in the medical literature to support the proposed IN volume per actuation and route of administration. These publications included (1) several articles that supported IN volumes of drug administration of up to 1 mL per nostril in pediatric patients (Buck 2013; Church et al. 2020; Del Pizzo and Callahan 2014; Triarico et al. 2019; Tsze et al. 2017), and (2) several articles evaluating other lipophilic small molecule drugs that supported similar BA when given intranasally in children as compared to healthy adults (Christensen et al. 2004; Miller et al. 2018), or rapidity of onset of when given intranasally in young children as compared to intravenously (Sharma and Harish 2013).

Label comprehension and human factors studies that included adolescent subjects support use of the product by adolescents. The label comprehension study, which included adolescent subjects down to age 15 years, had been conducted by FDA to support nonproduct-specific aspects of the DFL. Adolescents, who composed nearly 20% of the overall sample, generally outperformed the adult opioid user and associate group and the adult general population group across most primary and secondary endpoints. The Applicant also conducted an HFVS that included adolescent participants between 12 and 17 years of age, 30% of whom had limited literacy.

The Division of Pediatric and Maternal Health was consulted to evaluate the adequacy of the pediatric assessment to support approval in the full pediatric age range and found that the pediatric assessment addressed all of the key issues. Please see Dr. Ndidi Nwokorie's review dated April 3, 2023, for more information (DARRTS Reference ID: 5152520). The product was discussed by the Pediatric Research Committee on March 28, 2023.

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

Refer to the prescribing information for the reference product, NDA 016636.

In summary, naloxone should be used during pregnancy only if clearly needed. No adequate and well-controlled studies in pregnant women exist. Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area of mg/m^2) demonstrated no embryotoxic or teratogenic effects due to Narcan. Risk-benefit must be considered before naloxone is administered to a pregnant woman who is known or suspected to be opioid-dependent because maternal dependence may often be accompanied by fetal dependence. Caution should be exercised when naloxone is administered to a nursing woman. No additional labeling is needed.

9. Product Quality

Approval

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 217722 with respect to CMC and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. Therefore, OPQ recommends approval of this NDA from a quality perspective.

Critical CMC issues resolved during the review are described below.

Drug Substance

The drug substance supplier, (b) (4) The issue was resolved based on HRT's response that prior to cessation of manufacturing activities at (b) (4) HRT secured enough naloxone hydrochloride to support the commercial manufacture of the drug product for several years. This drug substance is in inventory at the drug product manufacturer, Catalent Pharma Solutions, in Morrisville, NC. Catalent is responsible for continuing good manufacturing practice activities (e.g., retest testing for the active pharmaceutical ingredient).

(b) (4)

Drug Product

RiVive (naloxone HCl 3 mg/0.1 mL) nasal spray is proposed as a nonprescription naloxone product. It is a drug-device combination product with a new pharmaceutical formulation of the active substance naloxone. The drug product portion is an aqueous, nonsterile, (b) (4) nasal solution. The product is a single-use, disposable device intended to administer a single, fixed dose of naloxone to the IN cavity of a patient. The primary container closure consists of a glass vial and stopper designed to contain the drug product in the (b) (4)

Components and composition, manufacturing controls, drug product critical quality attributes and in-process controls, microbiological controls, and facilities sections of the application were reviewed, and they are adequate from the CMC perspective. Major issues encountered during review are discussed below.

The microbiological controls section of the drug product required significant communication with the Applicant throughout the review cycle, including many rounds of information requests and teleconferences (dated January 23, 2023, and February 1, 2023) related to microbiological quality attributes of the subject drug product, associated microbiological controls, and endpoint testing for the drug product manufacturing process. FDA noted a concern that the proposed drug product is aqueous (b) (4), which may have growth promotion capabilities. Thus, further information was required to understand whether the drug product maintains acceptable microbiological quality. The microbiology review was ultimately finalized following a review of an amendment dated May 5, 2023, covering results from the FDA-recommended growth promotion study of the formulation. Submitted results indicate that the drug product does not support microbial growth.

(b) (4) was also found to be adequate from a quality microbiology perspective.

Stability data from samples stored for 24 months at long-term conditions (25°C/60%RH) and 6 months at accelerated conditions (40°C/75%RH) show that there was an increase trending for (b) (4)

[redacted](b) (4). The Applicant's amendment to the NDA dated April 18, 2023, with a proposed shelf-life of 36 months was reviewed by the OPQ statistical team to determine if extrapolation of shelf-life from 24 months to 36 months is feasible. It was determined that the linear models done by the firm for [redacted](b) (4), as well as total degradation products are appropriate for a 36-month shelf-life. Thus, drug product shelf-life of 36 months is granted when stored at 20° to 25°C (68° to 77°F).

Regarding facilities, the drug product manufacturer (Catalent Pharma Solutions) was in Official Action Indicated status at the time of application submission and found acceptable only after a good manufacturing practice inspection. All other manufacturing facilities are in acceptable status.

9.1. Device or Combination Product Considerations

The combination product employs the [redacted](b) (4) drug delivery device designed and manufactured by [redacted](b) (4). This delivery device is a single-use, disposable device intended to administer a single, fixed dose of naloxone to the IN cavity. The combination product is composed of a filled vial, a plunger/stopper, a container holder, and the actuator subassembly.

The review covered all device related information including device description, labeling, design controls, risk analysis, design verification, and facilities and quality systems. All data provided in the review demonstrate adequate and reliable performance of the device to a 99.999% reliability, which is consistent with what is expected of emergency use devices. Stability data demonstrate adequate performance up to 36 months.

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

A request was submitted to the Office of Study Integrity and Surveillance (OSIS) for inspection as part of PDUFA preapproval clinical investigation and data validation of the pivotal BA study. In the consult memo, OSIS staff indicated that the analytical site and the clinical site had been inspected in [redacted](b) (4) and December 2022, respectively. OSIS determined that both sites were considered in compliance and concluded that new inspections were not needed for this application (OSIS memorandum, January 20, 2023; DARRTS Reference ID: 5112945).

There are two covered clinical studies in this NDA involving a total of six clinical investigators. An FDA form 3454 was submitted for each investigator with no disclosed financial interests or arrangements identified.

11. Advisory Committee Summary

A joint meeting of the Nonprescription Drugs Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee had been scheduled on March 20, 2023, to discuss the nonprescription marketing of the proposed product. However, based on the unanimous decision by the same advisory committee panel at a public meeting held in February 2023 to approve the prescription-to-nonprescription switch of another IN naloxone product for the same indication, the Division determined that an advisory committee meeting was no longer needed to discuss RiVive. An FR notice to this effect was published on March 2, 2023.

III. Additional Analyses and Information

12. Summary of Regulatory History

Table 21. Key Presubmission Meetings and Milestones

Activity/Date	Outcome
Type B pre-IND written response only (WRO) Aug 10, 2017	This was an initial meeting between the pre-IND application holder, Mundipharma Research Limited, and FDA to discuss development of a prescription naloxone nasal spray (b)(4) mg product. Applicant proposed and FDA agreed that an HFVS was needed to support NDA submission. FDA advised the Applicant to complete a comprehensive use-related risk analysis (URRA) to inform its HFVS and to submit the HFVS protocol for FDA review and feedback.
Type B pre-IND meeting Nov 15, 2018	This was an initial meeting between Harm Reduction Therapeutics, Inc. (HRT) and FDA to discuss development of a nonprescription naloxone nasal spray 3 mg product. HRT had acquired the U.S. rights to an intranasal (IN) naloxone product that was marketed under the name Nyxoid in the European Union and owned by Mundipharma Research Therapeutics. Extensive information was provided from a nonclinical, clinical pharmacology, pediatric, and device perspective. FDA informed the Applicant that an internal review of FDA's naloxone label comprehension study (LCS) was being completed on two model drug facts labels (DFLs). • FDA advised that if its independent review concluded that comprehension of the model DFL is adequate, then the Applicant would need to add information specific to its proposed device and conduct human factors testing to demonstrate the user interface supports safe and effective use of the product by the intended users. • As a response to the Applicant's inquiry on whether the draft DFL could be used or if the entire label should be retested, FDA stated that the device-specific instructions for the Applicant's proposed nonprescription product would need to be tested in an HFVS. • FDA also noted that if the Applicant decided not to use the draft DFL and developed its own label, then comprehension testing of the entire proposed label would need to be conducted.
Type B pre-IND - CMC WRO Mar 22, 2019	Extensive advice was provided from a CMC and device perspective regarding impurities, microbial growth assessment, stability testing, and device reliability testing.
IND opening Apr 14, 2020	HRT submitted its IND-opening protocol. A Study May Proceed letter was issued May 19, 2020.
Type C WRO Aug 5, 2020	Advice was provided from a CMC and device perspective regarding the proposed reliability study plan and quantity (duration) of stability and performance data to be submitted for NDA review.
Type B pre-NDA WRO May 4, 2021	Extensive advice about expected NDA content was provided from CMC, device, clinical pharmacology, nonclinical, clinical perspectives as well as recommendations to submit updated labeling for review and reiteration of FDA's recommendation to submit HFVS protocol prior to commencing the study.

Activity/Date	Outcome
Type C meeting Nov 10, 2021	FDA acknowledged the Applicant's HF formative study results, considered changes made to the DFL due to these study results, and made recommendations on the DFL changes as well as the evaluations needed in an HFVS.
Type C meeting June 9, 2022	FDA discussed the clinical pharmacology data generated as well as the nonclinical data requirements and safety data presentation in the NDA.
Fast Track Jul 1, 2022	FDA granted Fast Track designation.
Rolling submission Jul 27, 2022	FDA granted rolling submission.

Source: Reviewer generated
Abbreviations: CMC, chemistry, manufacturing, and controls; DFL, drug facts label; HF, human factor; HFVS, human factors validation study; IND, investigational new drug; NDA, new drug application

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, Harm Reduction Therapeutics, Inc., has submitted a 505(b)(2) new drug application (NDA) for RiVive nasal spray (naloxone hydrochloride 3 mg/0.1 mL). The proposed 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 original pharmacology or toxicology information was submitted in support of this NDA, and none was required. Of note, during the preinvestigational new drug (IND) meeting with the Applicant (IND 134611, type B meeting, December 20, 2018), no new nonclinical local tolerance studies were requested by the Division because no novel excipients were included in

the to-be-marketed formulation, and plans for adequate monitoring of local tolerance were included in the clinical studies. See Section 7.6.1 for additional information.

13.3.3. Recommendations

Approvability

Approvable from the nonclinical perspective.

Additional Nonclinical Recommendations

None

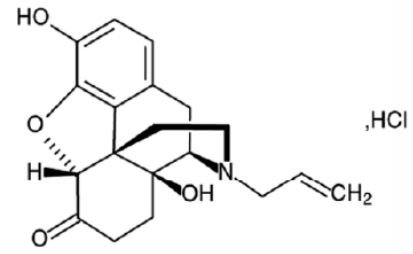
Labeling

Not applicable

13.4. Drug Information

13.4.1. Drug

Table 22. Drug Information

CAS registry number	51481-60-8
Generic name	Naloxone hydrochloride
Code name	N/A
Chemical name	Morphinan-6-one,4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride,(5)-, dihydrate 17-Allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate
Molecular formula/ Molecular weight	$C_{19}H_{21}NO_4$ • HCl $2H_2O$ / 399.87
Structure[1]	
Pharmacologic class	Opioid Antagonist (Established Pharmacological Class)

Source: Reviewer generated
[1] 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, 2023, PubChem 2023 Update, Nucleic Acids Res, 51(D1):D1373-d1380.

13.4.2. Relevant INDs, NDAs, BLAs and DMFs

Tables 23, 24, and 25 show relevant INDs, NDAs, and drug master files (DMFs) submitted to FDA.

Table 23. Relevant INDs

Information	Strength (Route)	Sponsor
IND 134611	Investigational doses (IN)	Harm Reduction Therapeutics

Source: Reviewer generated
Abbreviations: IN, intranasal; IND, investigational new drug

Table 24. Relevant NDAs

Information	Strength (Route)	Marketing Status	Sponsor
NDA 016636 NARCAN (naloxone HCl) injection	1 mg/mL (IV, IM, SC)	Withdrawn, FR effective	Adapt Pharma (formerly Endo)

Source: Reviewer generated
Abbreviations: FR, Federal Register; HCl, hydrochloride; IM, intramuscular; IV, intravenous; NDA, new drug application; SC, subcutaneous

Table 25. Relevant DMFs

DMF	Subject of DMF	Holder	LOA Filing Date
[redacted]	[redacted]	(b) (4)	Aug 31, 2022 Jul 11, 2022 Jul 11, 2022 Aug 16, 2022 Feb 18, 2021

Source: Reviewer generated
Abbreviations: DMF, drug master file; HCl, hydrochloride; USP, United States Pharmacopeia

13.4.3. Drug Formulation

The quantitative composition of the nonprescription drug product formulation is provided below (Table 26).

Table 26. Quantitative Composition of the Nonprescription Drug Product

Table 2.3.P.1-1. Composition of Naloxone HCl Nasal Spray 3 mg				
Component	**Quality Standard**	**Quantity per Dose (mg) #**	**Quantity per Vial (mg) §**	**Function**
Naloxone hydrochloride (b) (4)	USP	(b) (4)		Active ingredient
Trisodium Citrate dihydrate	USP			(b) (4)
Sodium chloride	USP			
Hydrochloric acid	NF			
Sodium hydroxide	NF			
(b) (4)				
Purified water	USP			
				(b) (4)

Source: Excerpted from the Applicant's NDA submission
Abbreviations: HCl, hydrochloride; NF, National Formulary; q.s. quantum sufficit; USP, United States Pharmacopeia

13.4.3.1. Comments on Novel Excipients

There are no novel excipients in the proposed nonprescription formulation (see Table 26).

13.4.3.2. Comments on Impurities/Degradants of Concern

During the review of the opening IND that supports this NDA (IND 134611, 30-day safety review; DARRTS Reference ID: 4607077), the pharmacology/toxicology (P/T) reviewer reported that the Applicant noted nine drug substance and drug product impurities, of which two were identified as being potentially genotoxic, (b) (4) and (b) (4) For confirmation, the chemical structures of all nine impurities were submitted to the FDA computational toxicology group (CDER/Office of Translational Sciences/Office of Clinical Pharmacology/Division of Applied Regulatory Science) for an assessment for genotoxicity using quantitative structure activity relationship ((Q)SAR) models (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). Three software programs were used: Derek Nexus 6.0.1, Leadscope Model Applier 2.3.3-1, and CASE Ultra 1.7.0.5. All (Q)SAR model outputs were reviewed with the use of expert knowledge to provide additional supportive evidence on the relevance of any positive, negative, conflicting, or inconclusive prediction, and to provide a rationale to support the final conclusion. The (Q)SAR assessment of mutagenic potential for the compounds is consistent with recommendations described in the International Council for Harmonisation (ICH) guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (March 2018) (IND 134611, 30-day safety review; DARRTS Reference ID: 4607077).

Two of the drug substance impurities, [redacted] (b) (4) and [redacted] (b) (4) were predicted to be positive by the FDA computational toxicology group, but not [redacted] (b) (4) (IND 134611, 30-day safety review; DARRTS Reference ID: 4607077). The P/T reviewer provided a risk assessment in the 30-day safety review (Table 27) and to the review team (opening IND internal safety meeting on May 6, 2020, and pre-NDA internal meeting on April 13, 2021) by quantifying the unit dose and daily exposure for each impurity, and integrated these exposures with the principles delineated in ICH M7(R1) (IND 134611, 30-day safety review; DARRTS Reference ID: 4607077).

According to ICH M7(R1), an impurity predicted to be mutagenic by computational methods (such as those used by the FDA computational toxicology group) can be controlled to a level that is considered to correspond with an exposure (i.e., acceptable intake) that is associated with no more than a negligible excess lifetime risk (<1 in 100,000, or 10^{-5}) of carcinogenicity or other toxic effects, which is known as the threshold of toxicological concern (TTC). The P/T reviewer applied the most conservative TTC of 1.5 mcg/day, which is typically applied in the case of a product intended to treat a condition that recurs chronically or chronic intermittently. The maximum daily exposure for each of the two impurities predicted to be genotoxic is less than the TTC, both individually and collectively (Table 28). Overall, the weight of evidence, including (1) the margin of exposure for each impurity relative to the TTC, and (2) the likely use of the drug product (acute use), is supportive of the proposed use of the drug product.

Table 27. Risk Assessment Table for the (Q)SAR Analysis of Drug Substance and Drug Product Impurities Conducted by FDA Computational Toxicology Group

PIND 134611	Sponsor- HRT001				FDA-Approved Nasal Product			FDA Computational Toxicology Group
Impurity	Specification Limit	Amount Per Dose	Total Exposure in Clinical Study (2 doses)	Maximum Daily Dose HRT001 as per ICHM7 Chronic Use Limit (1.5 ug/day)	Specification Limit	Amount Per Dose	Supporting Document	Prediction for Genotoxicity
[redacted] (b) (4)								Negative
								Positive
								Positive
								Negative
								Negative
								Negative
								Negative
								Negative
								Negative
[redacted] (b) (4)								

* Specification limit

Source: Excerpted from the P/T 30-day safety review for IND 134611
Abbreviations: MDD, maximum daily dose; PIND, preinvestigational new drug; (Q)SAR, quantitative structure activity relationship

Table 28. Drug Substance Impurity Risk Assessment

Drug Substance Impurity	Amount of Impurity Per Spray (Dose)	Maximum Daily Clinical Exposure From the Impurity (2 Sprays)	TTC	Exposure Margin: TTC/ Maximum Daily Clinical Exposure[1]	Number of Sprays (Dose) Per Day up to the TTC[2]
					(b) (4)

13.4.3.3. Comments on Leachables/Extractables

The are no safety concerns raised by findings from the container closure system leachable assay. The Applicant proposed an analytical evaluation threshold (AET) of 25 mcg/mL, with which P/T and CMC agree.[3]

For the leachable evaluation, the P/T reviewer considered two thresholds. Since this drug product is considered an acute use drug product, the safety concern threshold for a genotoxic or carcinogenic impurity is 120 mcg/day. The safety concern threshold is consistent with the principles described in ICH M7(R1) for less-than-lifetime exposures for carcinogenic impurities. The qualification threshold (QT) for non-genotoxic impurities is 5 mcg/day, which is consistent with the Product Quality Research Institute document (Norwood et al. 2006). To calculate the AET, the P/T reviewer relied upon the lowest applicable threshold, which is 5 mcg/day (QT threshold). Considering a 5 mcg/day QT threshold and a maximum daily dose volume of drug product of 200 µL/day (two sprays of 100 µL each is the volume of drug product associated with the maximum daily dose [MDD], see Section 13.4.4), the AET threshold relied upon by the Applicant of 25 mcg/mL is considered adequate.

The CMC reviewer concurs that there are no issues regarding the design or the results of the leaching study. The CMC reviewer also concurs with the proposed AET of 25 mcg/mL, based on a 5 mcg/day QT.[3]

For completeness, the P/T reviewer also quantified the daily exposure of each identified leachable (see Table 29). Considering the maximum daily dose of two sprays per day, which corresponds with a maximum daily drug product volume of 200 µL/day, none of the identified compounds report an exposure level above 1.5 mcg/day (see Table 30), which is the most conservative TTC (March 2018).

[3] Email correspondence with chemist Elise Luong, PhD (January 11, 2023, and March 28, 2023)

Table 29. Leachables Identified by the Applicant in the Drug Product

Characteristic	Limit of Detection (LOD) (µg/mL)	Largest value from stability studies
Volatile Leachables by HS GC-FID	(b) (4)	< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
Semi-Volatile Leachables by GCMS		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD

Source: Excerpted from the Applicant submission, nonclinical overview
Abbreviations: GCMS, gas chromatography mass spectrometry; HS-GC-FID, headspace gas chromatography with flame ionization detection

Table 30. Calculated Daily Exposure of Each Identified Leachable in the Drug Product

Leachable	Limit of Detection (mg/mL)	Daily Exposure (mg/day)[1]
(b) (4)		

Leachable	Limit of Detection (mg/mL)	Daily Exposure (mg/day)[1]
		(b) (4)

Source: Reviewer generated
[1] The daily exposure considers the maximum daily dose to be 2 sprays, which corresponds with a drug product volume of 200 µL/day

13.4.4. Proposed Clinical Population and Dosing Regimen

RiVive nasal spray is a single-use, drug-device combination product that delivers 3 mg naloxone hydrochloride with each 0.1 mL intranasal (IN) dose. The proposed indication is for the treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

The intended clinical population is adults and children, including neonates. The proposed initial dosing regimen is one spray into one nostril. However, repeat doses may be indicated and administered, depending on the clinical presentation and using a new nasal spray device, every 2 to 3 minutes until the patient wakes up. Note, for the toxicological risk assessment and safety evaluation, two doses are considered the maximum daily dose.

13.5. Studies Submitted

13.5.1. Studies Reviewed

None.

13.5.2. Studies Not Reviewed

For the NDA, the Applicant submitted links to the nonclinical toxicology and pharmacology studies submitted to the IND (134611) as required under 21 CFR 314.50. As stipulated therein, an NDA is required to contain all reports of investigations of the drug product sponsored by the applicant, as well as all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source).

The Applicant is relying upon the Agency's finding of safety and efficacy for NDA 016636 (Narcan [naloxone hydrochloride 0.4 mg/mL] injection) to support clinical efficacy as well as systemic safety of the proposed product. The reference product addressed systemic safety of naloxone at much higher systemic doses than those proposed for the intranasal product (RiVive) being considered in this NDA. Therefore, the submitted studies were not required to support approval and were not reviewed during the IND or NDA phases.

A comprehensive list of the studies submitted to IND 134611 is provided in this section in the tables below (Tables 31 to 36).

Table 31. Pharmacology Studies Submitted

Study Number	Title	Test System	GLP
Primary Pharmacodynamics			
OXUPR02-95.0	Opioid receptor binding and functionality	In vitro/Chinese hamster ovary cells and human embryonic kidney cells (CHO- K1 and HEK-293 cells)	No
Safety Pharmacology			
NDSE-585	In vitro cardiovascular safety (hERG)	Human embryonic kidney cells (HEK-293)	No

Source: Reviewer generated
Abbreviations: GLP, good laboratory practice; hERG, human ether-à-go-go-related gene

Table 32. Single-Dose Toxicology Studies Submitted

Study Number	Title	Test Article	Route/Method of Administration	Species/ Strain	Duration
KPC/17/PSB	Single Dose (Oral) Limit Test in the Rat	Naloxone HCl	Oral (gavage)	Rats/ Sprague-Dawley	Single-dose
KPC/18/PSB	Single Dose (Oral) Limit Test in the Rat	Naloxone HCl	Oral (gavage)	Mice/CD-1	Single-dose
KPC/19/PSB	Single Dose (Oral) Limit Test in the Rabbit	Naloxone HCl	Oral (gavage)	Rabbits/New Zealand white (NZW)	Single-dose
NDSE-727/ (b) (4)	An Acute Intranasal Probe Study with 5% Methylene Blue in Sprague Dawley Rats and Beagle Dogs (Non-GLP)	Methylene Blue (5%)	Intranasal	Rats/Sprague Dawley and Dogs/Beagle	Single-dose
NDSE-733/ (b) (4)	A 1-Day Intranasal Safety Study in Male Rats with Naloxone HCl Dihydrate	Naloxone HCl	Intranasal	Rats/Sprague Dawley	Single-dose

Source: Reviewer generated; all studies are GLP unless otherwise stated in the table
Abbreviations: GLP, good laboratory practice; HCl, hydrochloride

Table 33. Repeat-Dose Toxicity Studies Submitted

Study Number	Title	Test Article	Route/Method of Administration	Species/ Strain	Duration
NDSE-706 (b) (4)	2-Week Intermittent Intravenous Infusion Toxicity and Toxicokinetic Study With Naloxone HCl in Dogs	Naloxone HCl	Intravenous infusion	Dogs/Beagle	1-hour infusions (BID), 15-days
KPC/21/C	28-Day Dietary Range-Finding Study in the Mouse	Naloxone HCl	Oral (dietary)	Mice/CD-1	28-days
KPC/22/C	28-Day Dietary Range-Finding Study in the Rat (not GLP)	Naloxone HCl	Oral (gavage)	Rats/Sprague Dawley	28-days

Study Number	Title	Test Article	Route/Method of Administration	Species/ Strain	Duration
N003003E	Three Month Oral Toxicity Study of Naloxone in Mice	Naloxone HCl	Oral (dietary)	Mice/CD-1	13-weeks
KPC/23/C	13-Week Oral Toxicity Study in the Rat	Naloxone HCl	Oral (gavage)	Rats/Sprague Dawley	13-weeks
KPC/28/C	13-Week Oral Toxicity Study in the Dog	Naloxone HCl	Oral (capsules)	Dogs/Beagle	13-weeks
N003003D	Nine Month Oral Toxicity Study of Naloxone HCl in Dogs	Naloxone HCl	Oral (capsules)	Dogs/Beagle	39-weeks
KPC/24/87	52 Week Dietary Study in the Rat	Naloxone HCl	Oral (dietary)	Rats/Sprague Dawley	52-weeks
NDSE-736 (b) (4)	A 7-Day Intranasal Safety Study in Male Rats with Naloxone HCl Dihydrate	Naloxone HCl	Intranasal	Rats/Sprague Dawley	7-days

Source: Reviewer generated; all studies are GLP unless otherwise stated in the table
Abbreviations: BID, twice daily; GLP, good laboratory practice; HCl, hydrochloride

Table 34. Genotoxicity Studies Submitted

Study Number	Title	Test Article	Route/Method of Administration	Test System
70/8409	Ames Assay for Bacterial Reverse Mutagenicity	Naloxone chlorhydrate	In vitro	*S. typhimurium* bacteria cells
71/8409	Test for Gene Mutation in Mouse Lymphoma Cells Treated with Naloxone	Naloxone chlorhydrate	In vitro	Mouse lymphoma cells L5178Y/tk+/- with and without S9 activation
N003003C	Mammalian Cell Mutagenesis Testing of Naloxone HCL using the Mouse Lymphoma Cell Assay with Colony Sizing, with and without S9	Naloxone HCl	In vitro	Mouse lymphoma cells L5178Y/tk+/- with and without S9 activation
74/8506	Metaphase Analysis of Human Lymphocytes treated with Naloxone	Naloxone HCl	In vitro	Human lymphocytes from two donors, treated with and without S9
N003003A	Bone Marrow Micronucleus Test in Mice Treated with Naloxone (Single-dose)	Naloxone HCl	In vivo	Mice/CD-1

Source: Reviewer generated; all studies are GLP unless otherwise stated in the table
Abbreviations: GLP, good laboratory practice; HCl, hydrochloride

Table 35. Developmental and Reproductive Toxicity Studies

Study Number	Title	Route/Method of Administration	Species/ Strain	DART Segment	Dosing interval
KPC/32/86	Rat Fertility and General Reproductive Performance Study	Oral (gavage)	Rats/Sprague Dawley	One generation reproductive toxicology study (F_0-F_2)	Premating to lactation day 21
KPC/30/85	Rat Teratology Dose Ranging Study	Oral (gavage)	Rats/Sprague Dawley	Segment II	GD6-GD15
KPC/33/R	Rat Teratology Study	Oral (gavage)	Rats/Sprague Dawley	Segment II	GD6-GD15
KPC/34/R	Rat Peri-and Post Natal Study	Oral (gavage)	Rats/Sprague Dawley	Segment II and Segment III	GD15 to lactation day 21
KPC/31/85	Rabbit Teratology Dose Ranging Study	Oral (gavage)	Rabbits/Dutch	Segment II	GD6-GD18
KPC/35/R	Rabbit Teratology Study	Oral (gavage)	Rabbits/Dutch	Segment II	GD6-GD18

Source: Reviewer generated; all studies are GLP unless otherwise stated in the table
Abbreviations: DART, developmental and reproductive toxicity; GD, gestation day; GLP, good laboratory practice; HCl, hydrochloride

Table 36. Carcinogenicity Studies Submitted

Study Number	Title	Species/ Strain
ONU-N-009 (b) (4)	Naloxone Hydrochloride: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice	Mice/Tg.rasH2
N003003F	2-year Oral Oncogenicity Study of Naloxone HCl in Sprague-Dawley Rats	Rats/Sprague Dawley

Source: Reviewer generated; all studies are GLP unless otherwise stated in the table
Abbreviations: GLP, good laboratory practice; HCl, hydrochloride

13.5.3. Previous Reviews Referenced

Table 37. Previous IND/NDA Reviews Referenced

IND/NDA	Drug Product	Reviewer/Division	Discipline	Date Submitted to DARRTS
IND 134611	RiVive (naloxone HCl) nasal spray (3 mg)	Taro Akiyama, PhD/Office of Nonprescription Drugs (ONPD)	Pharmacology/ Toxicology (P/T)	May 12, 2020
NDA 208411	Narcan (naloxone HCl) nasal spray (4 mg)	Newton H. Woo, PhD / formerly in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)	Pharmacology/ Toxicology (P/T)	Nov 2, 2015

Source: Reviewer generated
Abbreviations: DARRTS, Document Archiving, Reporting, and Regulatory Tracking System; HCl, hydrochloride; IND, investigational new drug; NDA, new drug application

13.6. Pharmacology

13.6.1. Primary Pharmacology

No new pharmacology studies with IN naloxone were submitted or required for this NDA. The Applicant is relying upon FDA's finding of safety for NDA 016636 (Narcan [naloxone HCl] injection). An excerpt from the prescription 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.

13.6.2. Secondary Pharmacology

No new secondary pharmacology studies with IN naloxone were submitted or required for this NDA.

13.6.3. Safety Pharmacology

No new safety pharmacology studies with IN naloxone were submitted or required for this NDA.

13.7. Pharmacokinetics/ADME/Toxicokinetics

13.7.1. PK/ADME

No new PK/ADME studies with IN naloxone were submitted or required for this application.

13.7.2. Toxicokinetics

No new toxicokinetics studies with IN naloxone were submitted or required for this application.

13.8. General Toxicology

No new general toxicology studies with IN naloxone were submitted or required for this application. The Applicant is relying upon FDA's finding of safety for NDA 016636 (Narcan [naloxone HCl] injection).

Note, during the pre-IND meeting with the Applicant (IND134611, type B meeting, December 20, 2018; DARRTS Reference ID: 4363712) no new nonclinical local tolerance studies were requested by the Division because no novel excipients were included in the to-be-marketed formulation, and adequate monitoring of local tolerance in the clinical studies was conducted. Further, Narcan (naloxone HCl) nasal spray (NDA 208411), another IN product with a comparable maximum daily dose of naloxone HCl, was approved for prescription use in 2015. Since its approval, an abundance of clinical safety information has become available to support the local safety of the drug product. The IN nonclinical toxicity study submitted to IND134611 (study title: *A 1- and 7-Day Intranasal Safety Study in Male Rats with Naloxone HCl Dihydrate;* see Tables 32 and 33*)* was also reviewed for major safety issues. Note, the test article used for this IN study was naloxone dihydrate in saline, and not the proposed final formulation for the IN drug product. There were no test article-related findings reported in that study.

13.9. Genetic Toxicology

No new genetic toxicology studies with IN naloxone were submitted or required for this application. The Applicant is relying upon FDA's finding of safety for NDA 016636 (Narcan [naloxone HCl] injection).

An excerpt from the prescription label for Narcan (naloxone HCl) injection regarding genetic toxicity is provided below:

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

13.10. Carcinogenicity

No new carcinogenicity studies with IN naloxone were submitted. The Applicant is relying upon FDA's finding of safety for NDA 016636 (Narcan [naloxone HCl] injection). An excerpt from the prescription label for Narcan (naloxone HCl) injection regarding carcinogenicity follows: "Studies in animals to assess the carcinogenic potential of NARCAN have not been conducted."

13.11. Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies with IN naloxone were submitted or required for this application. The Applicant is relying upon FDA's finding of safety for NDA 016636 (Narcan [naloxone HCl] injection). An excerpt from the prescription label for Narcan (naloxone HCl) injection regarding developmental and reproductive toxicology follows:

"Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN."

Note, the exposure margin for the reproduction studies referenced above from the prescription label for Narcan (naloxone HCl) injection relied upon a clinical MDD of 10 mg/day. The MDD of the proposed IN drug product is only 6 mg/day. Therefore, when relying upon a clinical MDD of 6 mg/day, the exposure margin for the reproduction studies conducted in mice and rats is approximately 8-times and 16-times the dose of a 50 kg human, respectively. Further, 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. These studies were previously reviewed (see nonclinical review by Dr. Edward Tocus, dated May 12, 1969) and are summarized in the P/T review (dated November 2, 2015, DARRTS Reference ID: 3841831) for the original prescription Narcan (naloxone HCl) nasal spray (NDA 208411).

13.12. Integrated Summary and Safety Evaluation

No new pharmacology or toxicology information was submitted to this NDA, and none was required. The Applicant is relying upon FDA's finding of safety for NDA 016636 (Narcan [naloxone HCl] injection).

From the nonclinical perspective, this NDA is approvable.

14. Clinical Pharmacology

14.1. In Vitro Studies

Not applicable

14.2. In Vivo Studies

In this NDA, the Applicant submitted comparative bioavailability (BA) data referencing the prescription product approved under NDA 016636 (Narcan [naloxone hydrochloride] 0.4 mg/mL injection) to support clinical efficacy as well as systemic safety of the proposed product. Because the original NDA 016636 for Narcan injection was withdrawn not for reasons of safety or efficacy, the Applicant conducted the study HRT001-PK02 using Hospira Inc's abbreviated NDA (ANDA) 070256 naloxone HCl injectable product (0.4 mg/mL) to the original NDA 016636 given as a 0.4 mg/1 mL intramuscular (IM) injection as the comparator to establish a pharmacokinetic (PK) bridge. This approach of using generic products to the original NDA was deemed acceptable per the type B pre-IND WRO dated August 10, 2017. FDA further recommended that:

> The proposed product may be suitable to reverse opioid overdose in a community/out-of-hospital setting only if it demonstrates comparable or higher systemic exposure and

> comparable or quicker onset of action (i.e., by examining T_{max}, C_{max}, and partial AUC values) to the reference drug in your comparative bioavailability study. Since onset of action is critical for reversal of opioid overdose, your proposed product must demonstrate comparable or higher exposure to the comparator in the comparative BA study during early absorption phase.

Because the approved initial dose of injectable Narcan is from 0.4 mg to 2 mg in adults, using 0.4 mg IM naloxone injection as the reference was deemed acceptable to establish a scientific bridge, as noted in the type B pre-IND meeting minutes dated December 20, 2018. In addition, FDA recommended:

> Naloxone is typically redosed every 2 to 3 minutes if the patient does not respond. We note that you propose to collect several early PK samples before 10 min (e.g., at (b) (4)). To avoid time deviation due to frequent sampling, we recommend early sampling times of 2.5, 5, and 10 min, which have been used for previously approved naloxone products. Partial AUC values such as $AUC_{0-2.5}$, AUC_{0-5}, and AUC_{0-10} need to be calculated and compared.

Summary of Clinical Pharmacology Assessment

1. A single spray of RiVive in one nostril (i.e., a 3-mg dose) exhibited a median (min, max) T_{max} of 0.50 hour (0.17, 1.50 hour). The median (min, max) T_{max} value for 0.4 mg IM naloxone injection was 0.21 hour (0.08, 1.50 hour). The mean partial AUC values, $AUC_{0-2.5min}$, AUC_{0-5min}, and $AUC_{0-10min}$ during the early absorption phase for a single 3-mg dose of RiVive were 107%, 102%, and 142% of that for a single 0.4 mg IM naloxone injection. A single 3-mg dose of RiVive showed 2.98-fold greater C_{max} and 3.25- to 3.26-fold greater AUC_{0-t} and AUC_{0-inf} values than a single dose of 0.4 mg IM naloxone injection.
2. In the comparative BA study HRT001-PK02, a single 3-mg dose of RiVive showed comparable partial $AUC_{0-2.5min}$ and $AUC_{0-5min,}$ 42% greater $AUC_{0-10min}$ during the early absorption phase, and greater systemic exposure (C_{max}, AUC_{0-t} and AUC_{0-inf}) than the 0.4 mg IM naloxone injection. Because the approved initial dose of Narcan injectable (NDA 016636) is from 0.4 mg to 2 mg in adults via IV, IM or SC injection, the Applicant's proposed reliance on efficacy findings of Narcan injectable (NDA 016636) is warranted.
3. The Applicant also chose to conduct a study to evaluate the effect of face mask wearing on the absorption of the product. A single 3-mg dose of RiVive showed the same median T_{max} (0.5 hour) while wearing a KN95 mask compared to not wearing a KN95 mask. The mean $AUC_{0-2.5min}$ value was approximately 12% lower while wearing a KN95 mask than that while not wearing a KN95 mask. The mean AUC_{0-5min} and $AUC_{0-10min}$ values were approximately 34% and 35% greater, respectively, while wearing a KN95 mask than those while not wearing a KN95 mask. The AUC_{0-t}, AUC_{0-inf} and C_{max} values were similar for the proposed RiVive nasal spray in both conditions.

Summary of Pharmacokinetic Results

Comparative Bioavailability of Proposed RiVive Naloxone HCl Nasal Spray 3 mg and 0.4 mg IM Naloxone Injection (Results From Study HRT001-PK02 Part I)

The pivotal study HRT001-PK02 was a two-part investigation. Part I was a phase 1, open-label, single-dose, randomized, four-period, two-treatment, two-sequence, crossover, replicate

comparative BA study assessing RiVive (test product, treatment T) relative to 0.4 mg IM naloxone HCl injection (ANDA 070256 naloxone HCl injection 0.4 mg/mL from Hospira) (reference product, treatment R). The study was conducted in 36 healthy, nonsmoking male and female subjects under fasting condition. A replicate design (all participants received each study dose twice) was utilized to assess the within-subject variability and allow for a scaled bioequivalence statistical approach if within-subject variance was found to be greater than 30%.

Prior to dosing, subjects were randomized to one of two treatment sequences: Sequence 1 (TRTR) or Sequence 2 (RTRT). Test product was given via IN administration of one spray (single actuation) administered in one nostril. Subjects were asked to lie down in a supine position and remained in a supine position for at least 1 hour following drug administration. Subjects were advised to breathe through their mouths and not swallow during drug administration and for at least 1 minute after dosing completion. Subjects refrained from blowing their nose for 30 minutes following the administration of the nasal spray. Reference product was administered into the dorsogluteal muscle. To avoid any carryover effect, the washout period between treatments was at least 7 days.

Blood samples for determination of unconjugated (or free) naloxone concentrations in plasma were collected prior to dosing (0) and at 2.5, 5, 10, 12.5, 15, 30, and 45 minutes, and at 1, 1.5, 2, 4, 6, and 8 hours postdose for each treatment. PK analysis was performed on available data from subjects in the PK dataset using the actual postdose sample collection times. The PK parameters including $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}2.5min}$, $AUC_{0\text{-}5min}$, $AUC_{0\text{-}10min}$, C_{max} and T_{max} were estimated for unconjugated naloxone using a noncompartmental approach in Phoenix WinNonlin.

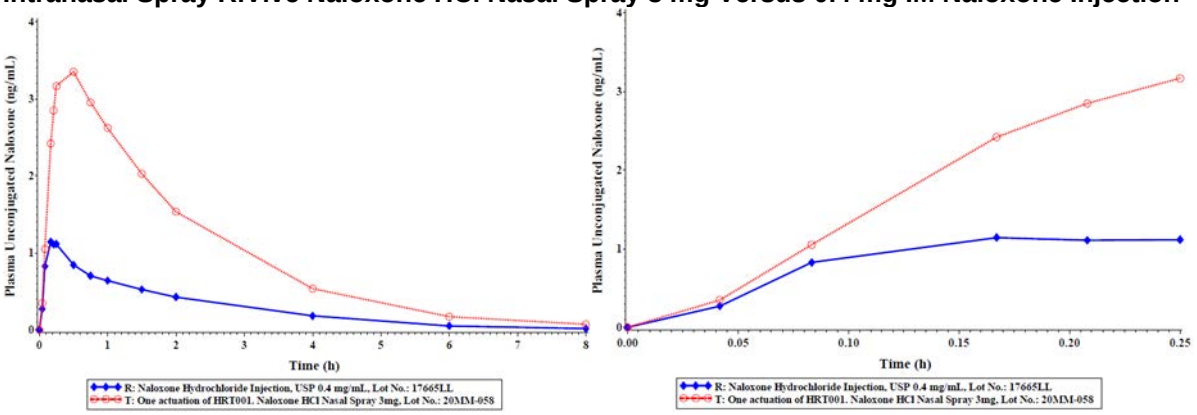
The mean naloxone plasma concentration-time profiles following a single dose of one IN spray of RiVive versus 0.4 mg IM naloxone injection are shown in Figure 11. Naloxone PK parameters are summarized in Table 38. The comparisons of naloxone C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}5min}$, $AUC_{0\text{-}2.5min}$, and $AUC_{0\text{-}10min}$ for the test and reference products are shown in Table 39.

The median (min, max) T_{max} values were 0.50 hours (0.17 to 1.50 hours) and 0.21 hours (0.08 to 1.50 hours) for the test and reference products, respectively. Mean half-life values of naloxone were 1.36 hours and 1.22 hours for the test and reference products, respectively (Table 38).

RiVive exhibited comparable naloxone concentrations during the early absorption phase (e.g., 2.5, 5 min postdose) and greater concentrations afterward than 0.4 mg IM naloxone injection (Figure 11 and Table 38). The mean partial AUC values, $AUC_{0\text{-}2.5min}$ and $AUC_{0\text{-}5min}$ during the early absorption phase for a single 3-mg dose of RiVive were 107% and 102% of that for a single 0.4 mg IM naloxone injection. The $AUC_{0\text{-}10min}$ value for the proposed RiVive was 42% greater than that of the reference product (Table 39).

The mean C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ values for RiVive were 2.98-, 3.25-, and 3.26-fold greater than those of the reference product because the geometric mean ratios (90% CI) for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ for RiVive/0.4 mg IM naloxone injection were 297.92% (263.76% - 336.51%), 325.45% (296.40% - 357.35%), and 325.76% (296.66% - 357.71%), respectively (Table 39).

Figure 11. Mean Plasma Concentration Time Profiles of Naloxone Following a Single Dose of One Intranasal Spray RiVive Naloxone HCl Nasal Spray 3 mg Versus 0.4 mg IM Naloxone Injection



Source: Study report HRT001-PK02 Figures 11-1 and 11-3; Plot on the left: 0-8 hours and plot on the right: 0-0.25 hour. R1: n = 36; R2: n = 35; T1: n = 36; T2: n = 36/Replicate Measures
Abbreviations: HCl, hydrochloride; IM, intramuscular

Table 38. Mean ± SD (%CV) Naloxone Pharmacokinetic Parameters for RiVive Naloxone HCl Nasal Spray 3 mg and 0.4 mg IM Naloxone Injection, Study HRT001-PK02 Part I

PK Parameter	RiVive Naloxone HCl Nasal Spray 3 mg (N=72)	0.4 mg IM Naloxone Injection (N=71)[1]
T_{max} (h)[2]	0.50 (0.17 – 1.50)	0.21 (0.08 – 1.50)
C_{max} (ng/mL)	4.07 ± 2.1395 (52.57%)	1.4052 ± 0.8148 (57.98%)
AUC_{0-t} (ng.h/mL)	7.4983 ± 3.2412 (43.23%)	2.1650 ± 0.4985 (23.02%)
AUC_{0-inf} (ng.h/mL)	7.6449 ± 3.2957 (43.11%)	2.2037 ± 0.5020 (22.78%)
$AUC_{0-2.5min}$ (ng.h/mL)	0.0063 ± 0.0134 (211.16%)[1]	0.0048 ± 0.0109 (225.45%)
AUC_{0-5min} (ng.h/mL)	0.0349 ± 0.0589 (168.68%)[3]	0.0271 ± 0.0395 (145.52%)[4]
$AUC_{0-10min}$ (ng.h/mL)	0.1791 ± 0.2097 (117.14%)[1]	0.1087 ± 0.0961 (88.49%)[5]
K_{el} (1/h)	0.5243 ± 0.0879 (16.77%)	0.5803 ± 0.0840 (14.48%)
$T_{1/2}$ (h)	1.36 ± 0.25 (18.18%)	1.22 ± 0.18 (14.77%)

Source: Study report HRT001-PK02 Table 14-2.
[1] n=71
[2] Reported as median (min, max)
[3] n=67
[4] n=66
[5] n=70
Note: For all parameters in Treatment R, one subject did not complete period 4 due to discontinuation from the study. Data were excluded for calculating partial AUCs ($AUC_{0-2.5min}$, AUC_{0-5min}, $AUC_{0-10min}$) due to samples missed or taken late.
Abbreviations: CV, coefficient of variation; HCl, hydrochloride; IM, intramuscular; PK, pharmacokinetic; SD, standard deviation

Table 39. Statistical Analysis (Average Bioequivalence) of Naloxone AUC_{0-t}, AUC_{0-inf}, C_{max}, AUC_{0-5min}, $AUC_{0-2.5min}$, and $AUC_{0-10min}$ After an Intranasal Administration of RiVive Naloxone HCl Nasal Spray 3 mg and 0.4 mg IM Naloxone Injection

	Geometric Least Squares Means			
Parameter	RiVive Naloxone HCl Nasal Spray 3 mg	0.4 mg IM Naloxone injection	Ratio (T/R) (%)	90% CI
C_{max} (ng/mL)	3.6963	1.2407	297.92	263.76–336.51
AUC_{0-t} (ng.h/mL)	6.8482	2.1042	325.45	296.40–357.35
AUC_{0-inf} (ng.h/mL)	6.9821	2.1433	325.76	296.66–357.71
$AUC_{0-2.5min}$ (ng.h/mL)	0.0025	0.0023	106.89	78.85–144.89
AUC_{0-5min} (ng.h/mL)	0.0160	0.0157	101.51	75.88–135.80
$AUC_{0-10min}$ (ng.h/mL)	0.1155	0.0814	141.87	114.97–175.07

Source: Study report HRT001-PK02 Table 11-3
Abbreviations: CI, confidence interval; HCl, hydrochloride; IM, intramuscular; R, reference product; T, test product

In addition, the Applicant conducted a reference scaled average bioequivalence analysis for PK parameters with the within-subject standard deviation for the reference drug product (sWR) ≥0.294. The geometric mean ratios for $AUC_{0\text{-}2.5min}$ and $AUC_{0\text{-}5min}$ values between the proposed 3 mg RiVive nasal spray and 0.4 mg IM naloxone injection were 113.02% and 95.16%, respectively (Table 40).

Table 40. Statistical Analysis (Reference Scaled Average Bioequivalence) of Naloxone $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, $AUC_{0\text{-}5min}$, $AUC_{0\text{-}2.5min}$, and $AUC_{0\text{-}10min}$ After an Intranasal Administration of RiVive Naloxone HCl Nasal Spray 3 mg and 0.4 mg IM Naloxone Injection

Reference-Scaled Average Bioequivalence				
Parameter	*Ratio (%)*	*Intra-Subject Within-Reference Std. Deviation (sWR)*	*Intra-Subject Within-Reference CV%*	*RSABE Criterion*
AUC_t	.	0.094	9.38	N/A
AUC_{inf}	.	0.091	9.11	N/A
C_{max}	303.83	0.395	41.12	1.3933
$AUC_{0\text{-}5min}$	95.16	0.969	124.81	-0.4782
$AUC_{0\text{-}2.5\ min}$	113.02	0.802	95.01	-0.2216
$AUC_{0\text{-}10min}$	145.99	0.611	67.29	0.0720

Treatment T (Test)	One actuation of HRT001. Naloxone HCl Nasal Spray 3mg, Lot No.: 20MM-058 (Harm Reduction Therapeutics, USA)
Treatment R (Reference)	Naloxone Hydrochloride Injection, USP 0.4 mg/mL, Lot No.: 17665LL (Hospira Inc., USA)

Source: Study report HRT001-PK02 Table 11-3
Abbreviations: CV, coefficient of variation; HCl, hydrochloride; IM, intramuscular; N/A, not applicable

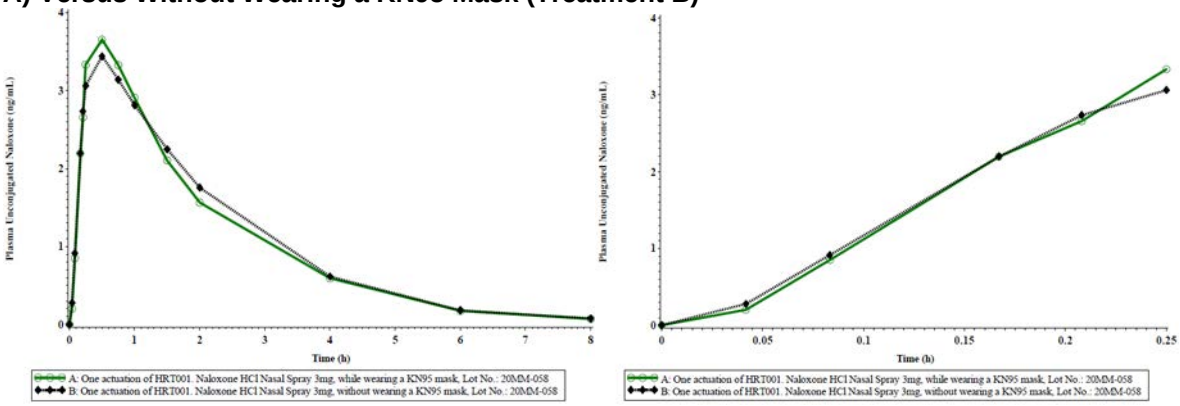
Reviewer comment: Note that an earlier comparative BA study, HRT001-PK01, had been conducted; however, the Applicant identified deficiencies in the study's execution, including numerous operational and bioanalytical shortcomings. Thus, the PK results from this study are not used to support the scientific bridge for efficacy. The Applicant conducted a second study, HRT001-PK02, which was adequately conducted and suitable for use as the pivotal study to support approval of RiVive.

Effects of KN95 Mask-Wearing on the Bioavailability of Proposed RiVive Naloxone HCl Nasal Spray 3 mg (From Study HRT001-PK02 Part II)

Study HRT001-PK02 Part II was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover relative bioavailability study conducted in 21 healthy volunteers under fasting condition to assess the impact of prolonged mask-wearing on the absorption of RiVive naloxone HCl nasal spray 3 mg. In each period, subjects received either one actuation (3 mg naloxone HCl) of RiVive in the right nostril after wearing a KN95 mask for at least 24 hours prior to drug administration and up to the time of the last PK blood sample of the period, or one actuation (3 mg naloxone HCl) of RiVive in the right nostril after not wearing a mask for the previous 24 hours. Out of 24 subjects enrolled in Part II, 21 subjects completed the study.

RiVive showed the same median T_{max} (0.5 hours) with and without wearing a KN95 mask (Table 41). The mean $AUC_{0\text{-}2.5min}$ value was approximately 12% lower for the test product while wearing a KN95 mask compared to the test product without wearing a KN95 mask ($AUC_{0\text{-}2.5min}$ ratio = 88.22%). The mean $AUC_{0\text{-}5min}$ and $AUC_{0\text{-}10min}$ values for the test product while wearing a KN95 mask were approximately 34% and 35% greater than those of the test product without wearing a KN95 mask ($AUC_{0\text{-}5min}$ ratio = 134.23% and $AUC_{0\text{-}10min}$ ratio = 135.48%). The $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max} values were similar for the test product in the KN95 mask condition and no KN95 mask condition ($AUC_{0\text{-}t}$ ratio = 97.55%; $AUC_{0\text{-}inf}$ ratio = 97.31%; C_{max} ratio = 103.66%; Table 42).

Figure 12. Mean Plasma Concentration Time Profiles of Naloxone Following a Single Dose of One Intranasal Spray RiVive Naloxone HCl Nasal Spray 3 mg While Wearing a KN95 Mask (Treatment A) Versus Without Wearing a KN95 Mask (Treatment B)



Source: Study report HRT001-PK02 Figures 11-5 and 11-7; Plot on the left: 0-8 hours and plot on the right: 0-0.25 hour
Abbreviations: HCl, hydrochloride

Table 41. Mean ± SD (%CV) Naloxone Pharmacokinetic Parameters for RiVive Naloxone HCl Nasal Spray 3 mg While Wearing a KN95 Mask (Treatment A) Versus Without Wearing a KN95 Mask (Treatment B)

PK Parameter	RiVive Naloxone HCl Nasal Spray 3 mg While Wearing a KN95 Mask (Treatment A) (N=20)	RiVive Naloxone HCl Nasal Spray 3 mg Without Wearing a KN95 Mask (Treatment B) (N=20)
T_{max} (h)[1]	0.50 (0.21–1.00)	0.50 (0.21–1.50)
C_{max} (ng/mL)	4.1630±1.5371 (36.92%)	4.0775±1.7783 (43.61%)
$AUC_{0\text{-}t}$ (ng.h/mL)	7.9443±2.6404 (33.24%)	8.1177±3.1734 (39.09%)
$AUC_{0\text{-}inf}$ (ng.h/mL)	8.0918±2.7247 (33.67%)	8.2702±3.2039 (38.74%)
$AUC_{0\text{-}2.5min}$ (ng.h/mL)	0.0042±0.0042 (100.64%)	0.0058±0.0076 (132.78%)
$AUC_{0\text{-}5min}$ (ng.h/mL)	0.0260±0.0179 (68.66%)	0.0305±0.0329 (107.86%)
$AUC_{0\text{-}10min}$ (ng.h/mL)	0.1534±0.0902 (58.79%)	0.1601±0.1552 (96.96%)
K_{el} (1/h)	0.5547±0.0849 (15.30%)	0.5309±0.0972 (18.31%)
$T_{1/2}$ (h)	1.28±0.22 (17.04%)	1.36±0.34 (25.0%)

Source: Study report HRT001-PK02 part II Table 14-4
[1] Reported as median (min, max)
Abbreviations: CV, coefficient of variation; HCl, hydrochloride; SD, standard deviation

Table 42. Statistical Analysis of Naloxone AUC_{0-t}, AUC_{0-inf}, C_{max}, AUC_{0-5min}, $AUC_{0-2.5min}$, and $AUC_{0-10min}$ After an Intranasal Administration of RiVive Naloxone HCl Nasal Spray 3 mg While Wearing a KN95 Mask (Treatment A) and With Wearing a KN95 Mask (Treatment B)

Parameter	*Trt*	*n*[a]	*Arithmetic Mean (CV%)*	*Geometric Mean*[b]	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**A**	20	7.9443 (33)	7.4834	**A vs B**	97.55	90.22 - 105.47	14.2
*(hr*ng/mL)*	**B**	20	8.1177 (39)	7.6712				
AUC_{inf}	**A**	20	8.0918 (34)	7.6097	**A vs B**	97.31	90.02 - 105.19	14.2
*(hr*ng/mL)*	**B**	20	8.2702 (39)	7.8199				
C_{max}	**A**	20	4.1630 (37)	3.9540	**A vs B**	103.66	92.70 - 115.91	20.5
(ng/mL)	**B**	20	4.0775 (44)	3.8144				
AUC_{0-5min}	**A**	20	0.0260 (69)	0.0193	**A vs B**	134.23	78.06 - 230.80	128
*(hr*ng/mL)*	**B**	20	0.0305 (108)	0.0144				
$AUC_{0-2.5min}$	**A**	20	0.0042 (101)	0.0026	**A vs B**	88.22	43.52 - 178.86	173
*(hr*ng/mL)*	**B**	20	0.0058 (133)	0.0029				
$AUC_{0-10min}$	**A**	20	0.1534 (59)	0.1283	**A vs B**	135.48	88.13 - 208.25	91.5
*(hr*ng/mL)*	**B**	20	0.1601 (97)	0.0947				

[a] Data were excluded in the statistical analysis due to following reasons:
All parameters: Three (3) subjects did not complete period 2 due to discontinuation from the study.
The 5 minute sample was taken late for 1 subject in period 2.
[b] Calculated from the Least Squares Means from the Proc Mixed model.

Treatment A (Test)	One actuation of HRT001. Naloxone HCl Nasal Spray 3mg, while wearing a KN95 mask, Lot No.: 20MM-058 (Harm Reduction Therapeutics, USA)
Treatment B (Reference)	One actuation of HRT001. Naloxone HCl Nasal Spray 3mg, without wearing a KN95 mask, Lot No.: 20MM-058 (Harm Reduction Therapeutics, USA)

Source: Study report HRT001-PK02 Table 11-4
Abbreviations: CV, coefficient of variation; HCl, hydrochloride

Reviewer comment: Part II of study HRT001-PK02 to evaluate the effect of wearing a mask is not considered as the pivotal evidence to support approval of this product. The Applicant chose to conduct the study at its discretion. The study provides information to demonstrate that wearing a mask may not affect absorption of the product.

14.3. Bioanalytical Method Validation and Performance

The bioanalytical high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) method for the determination of unconjugated naloxone concentrations in human plasma in study 2021-5119 (study HRT001-PK02) was adequately validated. The lower limit of quantitation is 0.0100 ng/mL. The standard calibration range was from 0.0100 ng/mL to 8.00 ng/mL. The assay precision (%CV) and accuracy (% of nominal concentrations) were from 1.1% to 4.5% and from 97.7% to 98.8% for Part I and from 1.0% to 4.0% and from 98.7% to 104.0% for Part II, respectively.

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

See Section 7.6 for a review of the clinical safety database.

Section 7.6.2.2 discusses the Applicant's postmarketing safety analysis of FDA Adverse Event Reporting System and VigiBase. The following tables list the preferred terms used by the Applicant to evaluate the special topics of rebound opioid toxicity (Table 43), use errors (Table 44), and opioid withdrawal (Table 45).

Table 43. List of Preferred Terms Used to Evaluate the Topic of Rebound Opioid Toxicity

Preferred Terms	
Acute cardiac event	Disturbance in attention
Acute respiratory distress syndrome	Dyskinesia
Acute respiratory failure	Dyspnea
Amnesia	Hypopnea
Aphasia	Hypotension
Apnea	Lack of spontaneous speech
Aspiration	Loss of consciousness
Blood pressure decreased	Noncardiogenic pulmonary edema
Brain death	Overdose
Brain injury	Oxygen saturation decreased
Cardiac arrest	Pulmonary edema
Cardiac failure	Pulse absent
Cardio-respiratory arrest	Respiration abnormal

Preferred Terms	
Chest pain	Respiratory arrest
Circulatory collapse	Respiratory depression
Coma	Respiratory failure
Confusional state	Respiratory rate decreased
Cyanosis	Seizure
Death	Terminal state
Depressed level of consciousness	Unresponsive to stimuli
Disorientation	Vomiting

Source: eCTD Module 5.3.5.3 Reports of Postmarketing Experience and Integrated Analysis of FAERS and VigiBase, submitted September 30, 2022; pp. 107–108.

Table 44. List of Preferred Terms Used to Evaluate the Topic of Errors (Error Subtype in Parentheses)

Preferred Terms	
Accidental exposure to product (User)	Premature delivery (User [if still using at the time of delivery])
Accidental overdose (User)	Prescription drug used without a prescription (User)
Circumstance or information capable of leading to device use error (Unknown)	Product administration error (User)
Device issue (Device subtype)	Product communication issue (Unknown)
Device use error (User)	Product container issue (Packaging)
Drug delivery system malfunction (Device)	Product delivery mechanism issue (Device)
Expired product administered (User)	Product expiration date issue (User)
Extra dose administered (User)	Product packaging difficult to open (Packaging)
Inappropriate schedule of product administration (Unknown)	Product prescribing issue (Prescriber)
Incorrect dose administered (User)	Product quality issue (Device)
Intentional overdose (User)	Product selection error (Unknown)
Intentional product misuse (User)	Product use complaint (User)
Intentional product use issue (User)	Product use in unapproved indication (Unknown)
Labelled drug-drug interaction medication error (Unknown)	Syringe issue (Device)
Lack of administration site rotation (User)	Unintentional use for unapproved indication (User)
Maternal exposure during pregnancy (Unknown)	Wrong schedule (User)
Off label use (Unknown)	Wrong technique in product usage process (User)
Premature baby (User [if still using at the time of delivery])	

Source: eCTD Module 5.3.5.3 Reports of Postmarketing Experience and Integrated Analysis of FAERS and VigiBase, submitted September 30, 2022; pp. 108–109.

Table 45. List of Preferred Terms Used to Evaluate the Topic of Opioid Withdrawal

Preferred Terms	
Abdominal pain	Myalgia
Acute pulmonary edema	Nausea
Asthenia	Nervousness
Blood pressure increased	Noncardiogenic pulmonary edema
Cardiac arrest	Piloerection
Chills	Pulmonary edema
Coma	Pyrexia
Crying	Restlessness
Death	Rhinitis
Diarrhea	Seizure
Drug withdrawal convulsions[1]	Sneezing

Preferred Terms	
Drug withdrawal headache[1]	Tachycardia
Drug withdrawal syndrome[1]	Tremor
Drug withdrawal syndrome neonatal[1]	Ventricular fibrillation
Encephalopathy	Ventricular tachycardia
Hyperhidrosis	Vomiting
Hyperreflexia	Withdrawal arrythmia[1]
Hypertension	Withdrawal catatonia[1]
Hypotension	Withdrawal syndrome[1]
Irritability	Yawning

Source: eCTD Module 1.11.4 Response to FDA Questions Received 7 November 2022, submitted November 16, 2022; Appendix 3.
[1] PTs included in the Standardized MedDRA Query for drug withdrawal

18. Clinical Virology

Not applicable

19. Clinical Microbiology

Not applicable

20. Mechanism of Action/Drug Resistance

Not applicable

21. Other Drug Development Considerations

Not applicable

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

See Section 10.

23. Labeling: Key Changes and Considerations

23.1. Approved Labeling Types

Upon approval of this NDA, the following labeling documents will be FDA-approved:

- Two-count outer carton
- Quick Start Guide (QSG)

- Immediate container (blister package) label
- Drug-delivery device label

23.2. Approach to the Labeling Review

This review is ongoing and will be concluded in the primary labeling review uploaded to DARRTS following the labeling negotiations with the Applicant.

The interdisciplinary scientist review team in DNPD I was tasked with assessing the labeling proposed in NDA 217722 to determine if it:

1. Follows the FDA model naloxone drug facts label (DFL) for nasal spray drug products
2. Follows nonprescription labeling regulations
3. Appropriately integrates approved naloxone prescription and nonprescription labeling elements for consumers (i.e., includes information in consumer-friendly terms so that the drug product is safe and effective when used as directed in the absence of supervision by a healthcare professional)
4. Aligns with the recommendations and determinations from other review disciplines

To encourage drug manufacturers to develop nonprescription naloxone drug products, FDA developed and validated a model naloxone DFL. The validation studies of the model label were announced in Federal Register (87 FR 68702, November 16, 2022), published in the *New England Journal of Medicine* (Cohen et al. 2020), and summarized in Section 6.3.2.

For this review, the proposed draft labeling for RiVive (naloxone hydrochloride 3 mg) nasal spray was preliminarily assessed to determine if the DFL was presented in accordance with relevant regulation and FDA guidances for industry *Labeling OTC Human Drug Products (Small Entity Compliance Guide)* (May 2009) and *Labeling OTC Human Drug Products — Questions and Answers* (December 2008).[4] The labeling outside the DFL, such as the information included in the QSG and principal display panel (PDP), was also assessed for suitability and to ensure safe and effective use of this product by consumers. Labeling revisions were ultimately recommended to improve the communication of important information outside of the DFL and to align the proposed labeling with the labeling requirements mentioned above and the guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation* (July 2002).

Reviewers from Division of Medication Error Prevention and Analysis II (DMEPA II) recommended revising the language for Steps 2 through 4 under the "***Directions***" heading in the DFL, based on findings from the Applicant's human factors validation study (HFVS). Reviewers from DMEPA II also recommended adding language outside of the DFL to reinforce messaging

[4] 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.

directed at proper usage of the nasal spray device. These recommendations were included in our labeling requests sent to the Applicant.

Table 46. Proposed Draft Labeling

Proposed Label	Date Submitted
2-count outer carton	Oct 28, 2022
Quick Start Guide (QSG)	Oct 28, 2022
Immediate container (blister package) label	Oct 28, 2022
Drug-delivery device label	Oct 28, 2022

Source: FDA reviewer generated table using labeling materials from NDA 217722 module 1.14.1.1 submitted October 28, 2022.

23.3. Review Issues

Nonprescription Labeling Regulation

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

Consumer-Friendly Labeling

The proposed labeling is largely based on FDA's model naloxone DFL, except for the addition of product-specific pictograms and instructions for administering RiVive (Steps 2 and 4) and changes to the Call 911 instructions (Step 3). The suitability of these changes was tested via an HFVS (refer to Sections 7.7.3 and 7.7.4 as well as the detailed review by DMEPA II dated May 2, 2023 [DARRTS Reference ID: 5166245]). The labeling outside of the DFL includes the PDP, QSG, 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 consumer studies, and FDA guidance for industry.

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 and lists the active ingredient, purpose, uses, warnings, directions, and inactive ingredients in accordance with 21 CFR 201.66(c) and (d). FDA developed a model naloxone DFL to encourage drug manufacturers to develop a nonprescription naloxone drug product (see Figure 13). The model naloxone DFL developed by FDA needs to be modified by an applicant to provide product-specific instructions. These changes would then be evaluated in an HFVS to demonstrate that users can safely and effectively use the drug product when following a sponsor's modified DFL. In this case, the Applicant modified Steps 2 through 4 of the "***Directions***." Content was also added to empty portions of the model naloxone DFL, including the content below the "***Other information***," "***Inactive ingredients***," and "***Questions***?" headings.

Figure 13. FDA Model Naloxone 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 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)

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.

The only substantive change to the "***Directions***" when comparing the Applicant's DFL with FDA's model naloxone DFL is the Applicant's use of instructions for use associated with a nasal spray drug delivery device (Figure 14). This change was accompanied with a pictogram (outside of the DFL) showing a hand holding a device that looks like the RiVive nasal spray device in the nostril of an apparently unconscious person. This labeling content was tested in an HFVS.

The Applicant also added the information listed below:

1. Storage conditions to the "***Other information***" section
2. A tamper-evident statement to the "***Other information***" section
3. The product's inactive ingredients to the "***Inactive ingredients***" section
4. A telephone number or resource that can be used to answer questions or record complaints to the "***Questions?***" section

The labeling contains a single warning that adequately warns consumers about adverse events 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.

Figure 14. Proposed RiVive Drug Facts Label

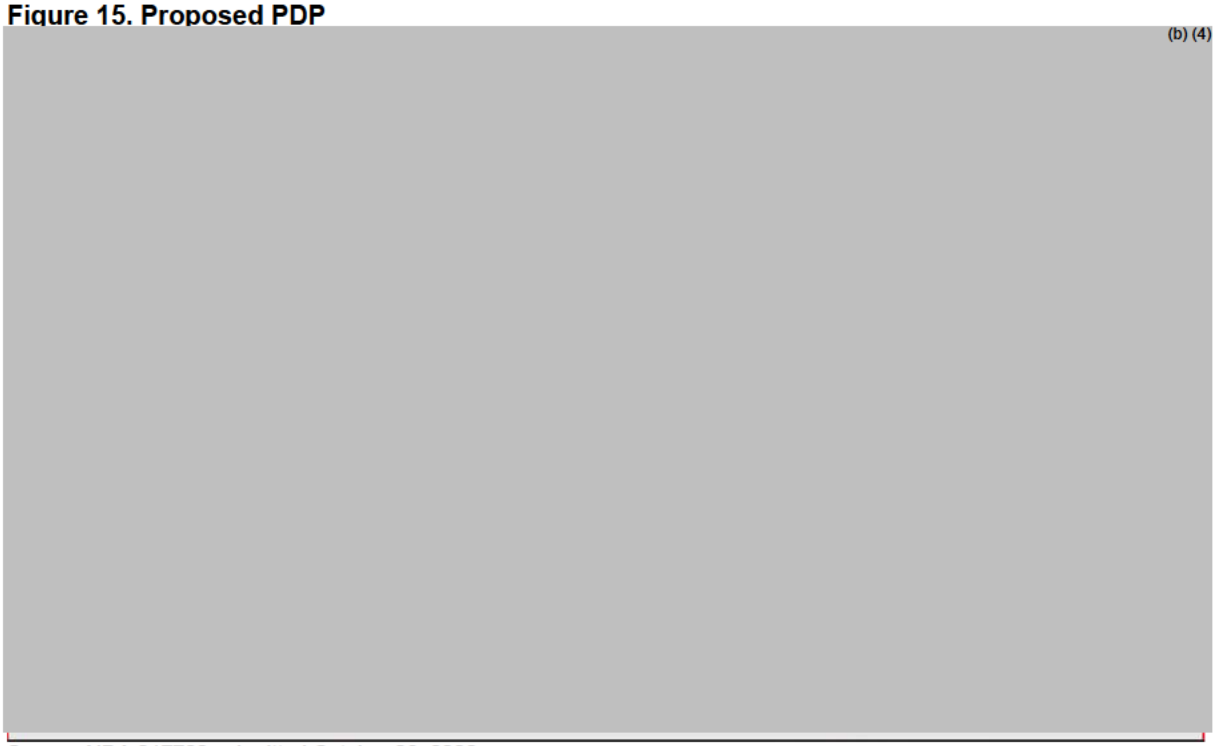
Source: NDA 217722 submitted October 28, 2022

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 [SOI]) 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 SOI and net quantity to assist consumers during drug selection.

The review team has also identified proposed labeling statements that must be changed to comply with regulation for consumer-friendly language and standardized formatting (Figure 15). For instance, the proposed SOI "(b) (4) " needs to be revised to "Naloxone HCl Nasal Spray 3 mg Emergency Treatment of Opioid Overdose" and increased in overall printed size. In addition, the proposed declaration of net quantity of contents statement needs to be modified to inform that each nasal spray contains only one dose and is for single use (i.e., "2 Single-Dose Nasal Spray Devices").

Figure 15. Proposed PDP



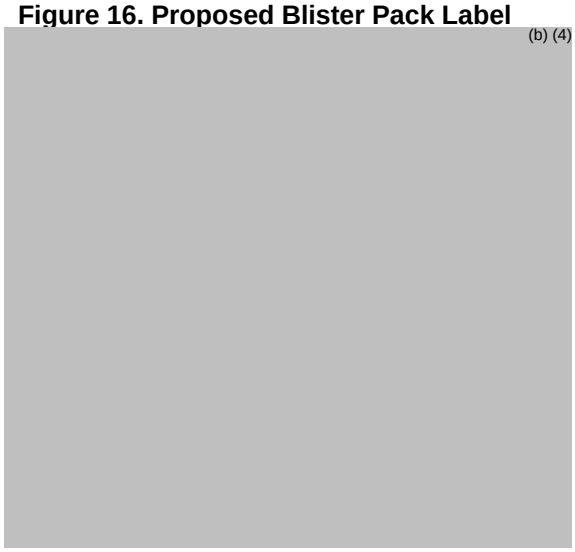
Source: NDA 217722 submitted October 28, 2022
Abbreviations: PDP, principal display panel

23.4.3. Blister Package Labeling

In addition to the outer carton (containing the PDP and DFL), the Applicant provided labels for a blister package (Figure 16) and for a QSG (Figure 17). The proposed blister package label is clean and simple. It contains the SOI, a statement to see the QSG enclosed in the blister package, and the distributor address. FDA requested the Applicant add important use and storage information to the blister package label because it is likely that some consumers will not

store/transport the blister package inside the outer carton. In the QSG, the Applicant replicated the directions from the DFL so that it readily provides users the directions without the need to search for the outer carton. FDA requested the Applicant revise its labeling to identify the QSG as “Directions” to help users quickly recognize that this insert contains instructions identical to the DFL.

Figure 16. Proposed Blister Pack Label



Source: NDA 217722 submitted October 28, 2022

Figure 17. Quick Start Guide

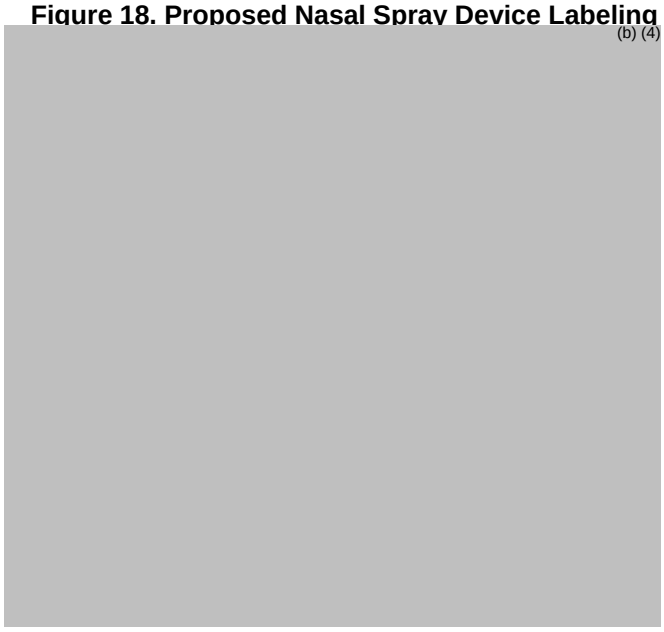
Source: NDA 217722 submitted October 28, 2022

23.4.4. Nasal Spray Device Labeling

The label placed directly on the nasal spray drug delivery device (Figure 18) needs further revision to include the statement “For use in the nose only” to further promote the correct route of administration. It also must include the expiration dating and lot number for cross-referencing the device with product quality data from the manufacturing site.

Figure 18. Proposed Nasal Spray Device Labeling

(b) (4)



Source: NDA 217722 submitted October 28, 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 the proposed labeling meets all applicable labeling regulations. Thus, 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. FDA has already requested 38 labeling revisions in the information request/advice letter sent April 21, 2023.

24. Postmarketing Requirements and Commitments

Not applicable

25. Financial Disclosure

Table 47. Covered Clinical Studies: HRT001-PK01, HRT001-PK02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator: Not applicable Sponsor of covered study: Not applicable		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 6		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

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27. Review Team

Table 48. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Trang Tran
Nonclinical reviewer	Chibueze Ihunnah
Nonclinical team leader	Donald Charles Thompson
Labeling reviewer	Robert Bahde
Labeling team leader	Kevin Lorick
Social scientist	Paul Jones
OCP reviewer	Wei Qiu
OCP team leader	Yun Xu
DMEPA II human factors reviewer	Millie Shah
DMEPA II human factors acting team leader	Colleen Little
DMEPA II human factors associate director	Lolita Sterrett
DMEPA II deputy division director	Chi-Ming (Alice) Tu
CMC reviewer	Swapan De
CMC team leader	Danae Christodoulou
CDRH reviewer	Dunya Karimi
CDRH team leader	Alan Stevens
DAAP clinical reviewer	Zachary Dezman
DAAP associate director for therapeutic review	Celia Winchell
Clinical reviewer	Jennifer Ah-Kee
Clinical team leader	Dorothy Chang
Cross-disciplinary team leader	Dorothy Chang
Division director (clinical, signatory)	Nushin Todd
Office director (clinical)	Theresa Michele

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 49. Additional Reviewers of Application

Office or Discipline	Name(s)
ORO/DRO-NPD	Dan Brum
DAAP	Zachary Dezman, Celia Winchell
OPQ	Elise Luong, Sithamalli Chandramouli, Suong Tran, Xueli Zhu, Erin Kim
Microbiology	Daniel Schu, Yeissa ChabrierRosello
OSE/DEPI	Tamra Meyer, Amy Seitz, Benjamin Booth
OSE/DMEPA II	Grace Jones, Ashleigh Lowery
OSE/DPV II	Lynda McCulley, Allison Lardieri
OSE/Drug Use	Corinne Woods, Jae Wook Yoo
DPMH	Ndidi Nwokorie, Mona Khurana

Abbreviations: ORO, Office of Regulatory Operations; DRO-NPD, Division of Regulatory Operations for Nonprescription Drugs; OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

27.1. Reviewer Signatures

Table 50. Signatures of Reviewers

See next page.

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Management Regulatory Project Manager	Trang Tran OND/ORO/ DRO-NPD	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Phong Pham signing on behalf of Trang Tran Phong T. Pham -S Digitally signed by Phong T. Pham -S Date: 2023.07.20 13:41:56 -04'00'				
Pharmacology/Toxicology Reviewer	Chibueze Ihunnah OND/ONPD/ NPDPTS	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Chibueze Ihunnah -S Digitally signed by Chibueze Ihunnah -S Date: 2023.07.18 10:22:54 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacology/ Toxicology Secondary Reviewer	Donald Charles Thompson OND/ONPD/ NPDPTS	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 5.1, 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: D Charles Thompson -S Digitally signed by D Charles Thompson -S Date: 2023.07.18 10:38:45 -04'00'				
Interdisciplinary Science Reviewer	Robert Bahde OND/ONPD/ DNPD I	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Robert J. Bahde -S Digitally signed by Robert J. Bahde -S Date: 2023.07.18 11:13:12 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Interdisciplinary Science Team Leader	Kevin Lorick OND/ONPD/ DNPD I	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 23	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	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.
Signature/date/time stamp: Kevin Lorick -S Digitally signed by Kevin Lorick -S Date: 2023.07.18 11:57:45 -04'00'				
Social Science Reviewer	Paul Jones OND/ONPD/ DNPD I	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Paul R. Jones -S Digitally signed by Paul R. Jones -S Date: 2023.07.18 14:16:32 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Reviewer	Wei Qiu OTS/OCP/DNP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Wei Qiu -S Digitally signed by Wei Qiu -S Date: 2023.07.18 13:41:24 -04'00'				
Clinical Pharmacology Team Leader	Yun Xu OTS/OCP/DNP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Yun Xu -S Digitally signed by Yun Xu -S Date: 2023.07.18 14:00:24 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Human Factors Reviewer	Millie Shah OSE/OMEPRM/ DMEPAII	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1, 2.1, 2.2, 3.1.2.3, 3.1.2.4, 7.7.3, 7.7.3.1, 7.7.3.2, 7.7.4, 7.7.4.1-7.7.4.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Millie Shah -S Digitally signed by Millie Shah -S Date: 2023.07.19 10:44:00 -04'00'				
Human Factors Team Leader	Colleen Little OSE/OMEPRM/ DMEPAII	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1, 2.1, 2.2, 3.1.2.3, 3.1.2.4, 7.7.3, 7.7.3.1, 7.7.3.2, 7.7.4, 7.7.4.1-7.7.4.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Colleen L. Little -S Digitally signed by Colleen L. Little -S Date: 2023.07.19 10:54:53 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Human Factors Associate Director	Lolita Sterrett OSE/OMEPRM/ DMEPAII	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1, 2.1, 2.2, 3.1.2.3, 3.1.2.4, 7.7.3, 7.7.3.1, 7.7.3.2, 7.7.4, 7.7.4.1-7.7.4.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Lolita Sterrett Digitally signed by Lolita Sterrett Date: 2023.07.19 12:08:25 -04'00'				
Human Factors Deputy Director	Chi-Ming (Alice) Tu OSE/OMEPRM/ DMEPAII	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1, 2.1, 2.2, 3.1.2.3, 3.1.2.4, 7.7.3, 7.7.3.1, 7.7.3.2, 7.7.4, 7.7.4.1-7.7.4.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Chi-ming Tu -S Digitally signed by Chi-ming Tu -S Date: 2023.07.19 13:02:59 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Product Quality Team Leader	Swapan De OPQ/ONDP/ DNDP III/ NDPB 6	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Swapan K. De -S Digitally signed by Swapan K. De -S Date: 2023.07.19 13:57:55 -04'00'				
Product Quality Branch Chief	Danae Christodoulou OPQ/ONDP/ DNDP III/ NDPB 6	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Danae D. Christodoulou -S Digitally signed by Danae D. Christodoulou -S Date: 2023.07.20 10:32:36 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CDRH General Engineer	Dunya Karimi CDRH/OPEQ/ OHTIII/DHTIIIC	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 9.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Dunya Karimi -S 2023.07.20 10:51:31 -04'00'				
CDRH Assistant Director	Alan Stevens CDRH/OPEQ/ OHTIII/DHTIIIC	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 9.1	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Alan Stevens 2023.07.20 12:44:41 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Rx Clinical/DAAP Reviewer	Zachary Dezman OND/ON/DAAP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Zachary D. Dezman -S Digitally signed by Zachary D. Dezman -S Date: 2023.07.18 08:40:58 -04'00'				
Rx Clinical/DAAP Associate Director for Therapeutic Review	Celia Winchell OND/ON/DAAP	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☒ Deficiencies preclude approval. ☒ Not applicable.	N/A
Signature/date/time stamp: Celia J. Winchell -S Digitally signed by Celia J. Winchell -S Date: 2023.07.20 13:18:38 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical/DNPD I Reviewer	Jennifer Ah-Kee OND/ONPD/ DNPD I	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections: 1, 2.1, 3, 4, 6, 7.3, 7.5, 7.6, 7.7.1, 7.7.2, 8.3, 17	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Jennifer L. Ah-kee -S Digitally signed by Jennifer L. Ah-kee -S Date: 2023.07.20 08:54:30 -04'00'				
Clinical/DNPD I Cross-Disciplinary Team Lead	Dorothy Chang OND/ONPD/ DNPD I	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A
Signature/date/time stamp: Dorothy Chang -S Digitally signed by Dorothy Chang -S Date: 2023.07.20 13:29:54 -04'00'				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical/DNPD I Division Director/ Signatory	Nushin Todd OND/ONPD/ DNPD I	☒ Benefit-Risk Assessment ☒ Interdisciplinary Assessment ☒ Additional Information and Analyses Sections:	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	N/A

Signature/date/time stamp:

Nushin Todd -S Digitally signed by Nushin Todd -S
Date: 2023.07.21 14:26:05 -04'00'

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
07/21/2023 05:44:50 PM

DOROTHY N CHANG
07/24/2023 08:26:46 AM

NUSHIN F TODD
07/28/2023 10:49:08 AM

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

Application number:	217722
Supporting document/s:	SD 2
Applicant's letter date:	10/28/22
CDER stamp date:	10/28/22
Product:	RiVive Nasal Spray (naloxone hydrochloride 3 mg/0.1 mL)
Indication:	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
Applicant:	Harm Reduction Therapeutics (HRT), Inc., 4800 Montgomery Lane, Suite 400, Bethesda, MD, USA
Review Division:	Division of Nonprescription Drugs I
Reviewer:	Chibueze A. Ihunnah, PhD, DABT
Team Leader:	D. Charles Thompson, RPh, PhD, DABT
Division Director:	Nushin Todd, MD, PhD
Project Manager:	CDR Trang Tran, PharmD, MBA

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 217722 are owned by Harm Reduction Therapeutics or are data for which HRT has obtained a written right of reference.
Any information or data necessary for approval of NDA 217722 that HRT 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 217722.

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Table of Tables

1 Executive Summary

1.1 Introduction

The Applicant, Harm Reduction Therapeutics, Inc., has submitted a 505(b)(2) NDA for RiVive Nasal Spray (naloxone hydrochloride 3 mg/0.1 mL). The proposed 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.

1.2 Brief Discussion of Nonclinical Findings

No new pharmacology or toxicology information was submitted in support of this NDA, and none was required. Of note, during the pre-IND meeting with the Applicant (IND 134611, Type B meeting, December 20, 2018) no new nonclinical local tolerance studies were requested by the Division because no novel excipients were included in the to-be-marketed formulation and plans for adequate monitoring of local tolerance were included in the clinical studies[1]. See the Integrated Summary for additional information.

1.3 Recommendations

1.3.1 Approvability

Approvable from the nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

Not Applicable.

[1] PIND 134611, Type B meeting with the Applicant, Meeting Minutes 12/20/18, Reference ID 4363712

2 Drug Information

2.1 Drug

CAS Registry Number: 51481-60-8

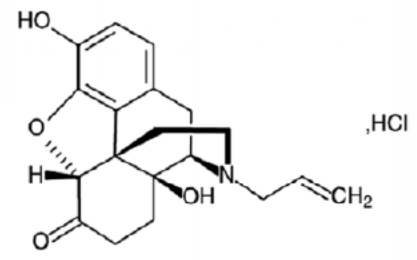
Generic Name: Naloxone Hydrochloride

Code Name: N/A

Chemical Name: Morphinan-6-one,4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-,hydrochloride,(5)-, dihydrate 17-Allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride
dihydrate

Molecular Formula/Molecular Weight: $C_{19}H_{21}NO_4 \bullet HCl\ 2H_2O$ / 399.87

Structure:



Pharmacologic Class: Opioid Antagonist (Established Pharmacological Class)

2.2 Relevant INDs, NDAs, BLAs and DMFs

Table 1. Relevant INDs

Information	Strength (Route)	Sponsor
IND 134611	Investigational doses (IN)	Harm Reduction Therapeutics

Table 2. Relevant NDAs

Information	Strength (Route)	Marketing Status	Sponsor
NDA 016636 NARCAN (Naloxone HCl) Injection	1 mg/mL (IV, IM, SC)	Withdrawn, FR Effective	Adapt Pharma (formerly Endo)

Table 3. Relevant DMFs

DMF	Subject of DMF	Holder	LOA Filing Date
		(b) (4)	8/31/22
			7/11/22
			7/11/22
			8/16/22
			2/18/21

*Referenced from the Applicant's NDA submission

2.3 Drug Formulation

The quantitative composition of the nonprescription drug product formulation is provided below.

Table 4. Quantitative Composition of the nonprescription drug product

Composition of the Drug Product

Table 2.3.P.1-1. Composition of Naloxone HCl Nasal Spray 3 mg				
Component	**Quality Standard**	**Quantity per Dose (mg) #**	**Quantity per Vial (mg) §**	**Function**
Naloxone hydrochloride (b) (4)	USP	(b) (4)		Active ingredient
Trisodium Citrate dihydrate	USP			(b) (4)
Sodium chloride	USP			
Hydrochloric acid	NF			
Sodium hydroxide	NF			
(b) (4)				
Purified water	USP			
				(b) (4)

*Excerpted from the Applicant's NDA submission

2.4 Comments on Novel Excipients

There are no novel excipients in the proposed nonprescription formulation (see Table 4).

2.5 Comments on Impurities/Degradants of Concern

During the review of the opening IND which supports this NDA (IND 134611, 30-day Safety Review), the pharmacology/toxicology (P/T) reviewer reported that the Applicant noted nine drug substance and drug product impurities, of which two were identified as being potentially genotoxic, (b) (4) and (b) (4) For confirmation, the chemical structures of all nine impurities were submitted to the FDA Computational Toxicology Group (CDER/OTS/OCP/DARS) for an assessment for genotoxicity using (Q)SAR models (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). Three software programs were used: Derek Nexus 6.0.1 (DX), Leadscope Model Applier 2.3.3-1 (LMA), and CASE Ultra 1.7.0.5 (CU). All (Q)SAR model outputs were reviewed with the use of expert knowledge to provide additional supportive evidence on the relevance of any positive, negative,

[2] IND 134611, Pharmacology and Toxicology 30-day safety review. Primary reviewer: Taro E. Akiyama, PhD. Reference ID 4607077

conflicting, or inconclusive prediction, and to provide a rationale to support the final conclusion. The (Q)SAR assessment of mutagenic potential for the compounds is consistent with recommendations described in the ICH guidance for industry, *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (March 2018)[3].

Two of the drug substance impurities, (b) (4) and (b) (4) were predicted to be positive by the FDA Computational Toxicology group, but not (b) (4) The P/T reviewer provided a risk assessment in the 30-day safety review (Table 5) and to the review team (5/6/2020 opening IND internal safety meeting, and 4/13/21 pre-NDA internal meeting) by quantifying the unit dose and daily exposure for each impurity, and integrated these exposures with the principles delineated in the ICH M7 guidance for genotoxic impurities[5].

According to ICH M7, an impurity predicted to be mutagenic by computational methods (such as those used by the FDA Comptox group) can be controlled to a level that is considered to correspond with an exposure (i.e., acceptable intake) that is associated with no more than a negligible excess lifetime risk (<1 in 100,00, or 10^{-5}) of carcinogenicity or other toxic effects, which is known as the threshold of toxicological concern (TTC). The P/T reviewer applied the most conservative TTC of 1.5 mcg/day, which is typically applied in the case of a product intended to treat a condition that recurs chronically or chronic intermittently. The maximum daily exposure for each of the two impurities predicted to be genotoxic is less than the TTC, both individually and collectively (Table 6). Overall, the weight-of-evidence, including (1) the margin of exposure for each impurity relative to the TTC, and (2) the likely use of the drug product (acute use), is supportive of the proposed use of the drug product.

[3] Ibid.
[4] Ibid.
[5] Ibid.

Table 5. Risk assessment table for the (Q)SAR analysis of drug substance and drug product impurities conducted by FDA Computational Toxicology Group (Excerpted from the 30-day safety review for IND 134611)

PIND 134611	Sponsor- HRT001				FDA-Approved Nasal Product			FDA Computational Toxicology Group
Impurity	Specification Limit	Amount Per Dose	Total Exposure in Clinical Study (2 doses)	Maximum Daily Dose HRT001 as per ICHM7 Chronic Use Limit (1.5 ug/day)	Specification Limit	Amount Per Dose	Supporting Document	Prediction for Genotoxicity
(b) (4)								Negative
								Positive
								Positive
								Negative
								Negative
								Negative
								Negative
								Negative
								Negative
(b) (4)								

*Excerpted from the P/T 30-day safety review for IND 134611

Table 6. Drug substance impurity risk assessment

Drug Substance Impurity	Amount of impurity per spray (dose)	Maximum daily clinical exposure from the impurity (2 sprays)	TTC	Exposure margin: TTC/ maximum daily clinical exposure[1]	Number of sprays (dose) per day up to the TTC[2]
(b) (4)					

2.6 Comments on Leachables/Extractables

The are no safety concerns raised by findings from the container closure system leachable assay. The Applicant proposed an Analytical Evaluation Threshold (AET) of 25 mcg/mL, which P/T and CMC agree with[6].

For the leachable evaluation, the P/T reviewer considered two thresholds. Since this drug product is considered an acute use drug product, the safety concern threshold (SCT) for a genotoxic or carcinogenic impurity is 120 mcg/day. The SCT is consistent with the principles described in the ICH *guidance for industry* M7(R1)[7] for less-than-lifetime exposures for carcinogenic impurities. The qualification threshold (QT) for non-genotoxic impurities is 5 mcg/day, which is consistent with the PQRI document[8]. To calculate the AET, the P/T reviewer relied upon the lowest applicable threshold, which is 5 mcg/day (QT threshold). Considering a 5 mcg/day QT threshold and a maximum daily dose volume of drug product of 200 μL/day (2 sprays of 100 μL each is the volume of drug product associated with the MDD, see section 2.7), the AET threshold relied upon by the Applicant of 25 mcg/mL is considered adequate.

The CMC reviewer concurs that there are no issues regarding the design or the results of the leaching study. The CMC reviewer also concurs with the proposed Analytical Evaluation threshold of 25 mcg/mL, based on a 5 mcg/day qualification threshold[9].

For completeness, the P/T reviewer also quantified the daily exposure of each identified leachable (see Table 7). Considering the maximum daily dose of 2 sprays per day, which corresponds with a maximum daily drug product volume of 200 μL/day, none of the identified compounds report an exposure level above 1.5 mcg/day (see Table 8), which is the most conservative threshold of toxicological concern (TTC)[10].

[6] Email correspondence with Chemist Elise Luong, PhD (1/11/23 and 3/28/23)
[7] ICH guidance for industry M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (2018)
[8] Product Quality Research Institute: Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products (2006)
[9] Email correspondence with Chemist Elise Luong, PhD (1/11/23 and 3/28/23)
[10] ICH guidance for industry M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (2018)

Table 7. Leachables identified by the Applicant in the drug product

Table 2.4-2. Leachables in Drug Product Registration Stability Batches 20MM-058, 20MM-059, 20MM-060

Characteristic	Limit of Detection (LOD) (µg/mL)	Largest value from stability studies
Volatile Leachables by HS GC-FID	(b) (4)	< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
Semi-Volatile Leachables by GCMS		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD
		< LOD

*Excerpted from the Applicant submission, nonclinical overview

Table 8. Calculated daily exposure of each identified leachable in the drug product

Leachable	Limit of Detection (µg/mL)	Daily Exposure (µg/day)*
(b) (4)		

* The daily exposure considers the maximum daily dose to be 2 sprays which corresponds with a drug product volume of 200 µL/day

2.7 Proposed Clinical Population and Dosing Regimen

RiVive Nasal Spray is a single-use, drug-device combination product that delivers 3 mg naloxone hydrochloride with each 0.1 mL intranasal dose. The proposed indication is for the treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

The intended clinical population is adults and children, including neonates. The proposed initial dosing regimen is one spray into one nostril. However, repeat doses may be indicated and administered depending on the clinical presentation, using a new nasal spray device, every two to three minutes, until the patient wakes up. Note, for the toxicological risk assessment and safety evaluation, two doses are considered the maximum daily dose.

2.8 Regulatory Background

Harm Reduction Therapeutics, Inc., (HRT, "the Applicant") submitted a new drug application (NDA) 217722 for RiVive Nasal Spray (naloxone hydrochloride 3 mg/0.1 mL) on October 28, 2022, in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

3 Studies Submitted

3.1 Studies Reviewed

None.

3.2 Studies Not Reviewed

For the NDA, the Applicant submitted links to the nonclinical toxicology and pharmacology studies submitted to the IND (134611). These studies were not reviewed during the IND or NDA phases because the Applicant is relying upon the Agency's finding of safety and efficacy for NDA 016636 (NARCAN [naloxone hydrochloride 0.4 mg/mL] Injection), to support clinical efficacy as well as systemic safety of the proposed product. Note, the Division advised the Applicant to submit these nonclinical studies as required under §314.50 (21 CFR 314.50). As stipulated therein, the NDA is required to contain all reports of investigations of the drug product sponsored by the applicant, as well as all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source.

A comprehensive list of the studies submitted to IND 134611 is provided in this section in the tables below.

Table 9. Pharmacology studies submitted

Primary Pharmacodynamics			
Study Number	**Title**	**Test system**	**GLP**
OXUPR02-95.0	Opioid receptor binding and functionality	*In vitro/* Chinese Hamster ovary cells and Human embryonic kidney cells (CHO-K1 and HEK-293 cells)	No
Safety Pharmacology			
Study Number	**Title**	**Test system**	**GLP**
NDSE-585	In vitro cardiovascular safety (hERG)	Human embryonic kidney cells (HEK-293)	No

Table 10. Single-dose toxicology studies submitted (All studies are GLP unless otherwise stated in the table)

Study Number	Title	Test article	Route/Method of Administration	Species/Strain	Duration
KPC/17/PSB	Single Dose (Oral) Limit Test in the Rat	Naloxone HCl	Oral (gavage)	Rats/ Sprague-Dawley	Single-dose
KPC/18/PSB	Single Dose (Oral) Limit Test in the Rat	Naloxone HCl	Oral (gavage)	Mice/CD-1	Single-dose
KPC/19/PSB	Single Dose (Oral) Limit Test in the Rabbit	Naloxone HCl	Oral (gavage)	Rabbits/New Zealand White (NZW)	Single-dose
NDSE-727/ (b) (4)	An Acute Intranasal Probe Study with 5% Methylene Blue in Sprague Dawley Rats and Beagle Dogs (Non-GLP)	Methylene Blue (5%)	Intranasal	Rats/Sprague Dawley and Dogs/ Beagle	Single-dose
NDSE-733/ (b) (4)	A 1-Day Intranasal Safety Study in Male Rats with Naloxone HCl Dihydrate	Naloxone HCl	Intranasal	Rats/Sprague Dawley	Single-dose

Table 11. Repeat-dose toxicity studies submitted (All studies are GLP unless otherwise stated in the table)

Study Number	Title	Test article	Route/Method of Administration	Species/Strain	Duration
NDSE-706 (b) (4)	2-Week Intermittent Intravenous Infusion Toxicity and Toxicokinetic Study with Naloxone HCl in Dogs	Naloxone HCl	Intravenous Infusion	Dogs/Beagle	1-hour infusions (BID), 15-days
KPC/21/C	28-day Dietary Range-Finding Study in the Mouse	Naloxone HCl	Oral (dietary)	Mice/ CD-1	28-days
KPC/22/C	28-day Dietary Range-Finding Study in the Rat (not GLP)	Naloxone HCl	Oral (gavage)	Rats/Sprague Dawley	28-days
N003003E	Three Month Oral Toxicity Study of Naloxone in Mice	Naloxone HCl	Oral (dietary)	Mice/ CD-1	13-weeks
KPC/23/C	13-week Oral Toxicity Study in the Rat	Naloxone HCl	Oral (gavage)	Rats/Sprague Dawley	13-weeks
KPC/28/C	13-week Oral Toxicity Study in the Dog	Naloxone HCl	Oral (capsules)	Dogs/Beagle	13-weeks
N003003D	Nine Month Oral Toxicity Study of Naloxone HCl in Dogs	Naloxone HCl	Oral (capsules)	Dogs/Beagle	39-weeks
KPC/24/87	52 Week Dietary Study in the Rat	Naloxone HCl	Oral (dietary)	Rats/Sprague Dawley	52-weeks
NDSE-736 (b) (4)	A 7-Day Intranasal Safety Study in Male Rats with Naloxone HCl Dihydrate	Naloxone HCl	Intranasal	Rats/Sprague Dawley	7-days

Table 12. Genotoxicity studies submitted (All studies are GLP unless otherwise stated in the table)

Study Number	Title	Test article	Route/Method of Administration	Test System
70/8409	Ames Assay for Bacterial Reverse Mutagenicity	Naloxone Chlorhydrate	*In vitro*	S. Typhimurium bacteria cells
71/8409	Test for gene mutation in mouse lymphoma cells treated with Naloxone	Naloxone Chlorhydrate	*In vitro*	Mouse Lymphoma cells L5178Y/tk+/- with and without S9 activation
N003003C	Mammalian Cell Mutagenesis Testing of Naloxone HCL using the Mouse Lymphoma Cell Assay with Colony Sizing, with and without S9	Naloxone HCl	*In vitro*	Mouse Lymphoma cells L5178Y/tk+/- with and without S9 activation
74/8506	Metaphase Analysis of Human Lymphocytes treated with Naloxone	Naloxone HCl	*In vitro*	Human lymphocytes from two donors, treated with and without S9
N003003A	Bone Marrow Micronucleus Test in Mice Treated with Naloxone (Single-dose)	Naloxone HCl	*In vivo*	Mice/ CD-1

Table 13. Developmental and reproductive toxicity studies (All studies are GLP unless otherwise stated in the table)

Study Number	Title	Route/Method of Administration	Species/Strain	DART Segment	Dosing interval[1]
KPC/32/86	Rat Fertility and General Reproductive Performance Study	Oral (gavage)	Rats/Sprague Dawley	One generation reproductive toxicology study (F_0-F_2)	Pre-mating to lactation day 21
KPC/30/85	Rat Teratology Dose Ranging Study	Oral (gavage)	Rats/Sprague Dawley	Segment II	GD6-GD15
KPC/33/R*	Rat Teratology Study	Oral (gavage)	Rats/Sprague Dawley	Segment II	GD6-GD15
KPC/34/R	Rat Peri-and Post Natal Study	Oral (gavage)	Rats/Sprague Dawley	Segment II and Segment III	GD15 to lactation day 21
KPC/31/85	Rabbit Teratology Dose Ranging Study	Oral (gavage)	Rabbits/Dutch	Segment II	GD6-GD18
KPC/35/R*	Rabbit Teratology Study	Oral (gavage)	Rabbits/Dutch	Segment II	GD6-GD18

1. GD = gestation day

Table 14. Carcinogenicity studies submitted (All studies are GLP unless otherwise stated in the table)

Study Number	Title	Species/ Strain
ONU-N-009 (b) (4)	Naloxone Hydrochloride: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice	Mice/Tg.rasH2
N003003F	2-year Oral Oncogenicity Study of Naloxone HCl in Sprague-Dawley Rats	Rats/Sprague Dawley

3.3 Previous Reviews Referenced

IND/NDA	Drug Product	Reviewer/Division	Discipline	Date submitted to DARRTS
IND 134611	RiVive (Naloxone HCl) Nasal Spray (3 mg)	Taro Akiyama, PhD/ Office of Nonprescription Drugs (ONPD)	Pharmacology/Toxicology (P/T)	5/12/20
NDA 208411	NARCAN (Naloxone HCl) Nasal Spray (4 mg)	Newton H. Woo, PhD / formerly in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)	Pharmacology/ Toxicology (P/T)	11/2/15

4 Pharmacology

4.1 Primary Pharmacology

No new pharmacology studies with intranasal naloxone were submitted or required for this NDA application. The Applicant is relying upon the Agency's finding of safety for NDA 016636 (NARCAN [Naloxone HCl] Injection). 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.

4.2 Secondary Pharmacology

No new secondary pharmacology studies with intranasal naloxone were submitted or required for this NDA application.

4.3 Safety Pharmacology

No new safety pharmacology studies with intranasal naloxone were submitted or required for this NDA application.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No new PK/ADME studies with intranasal naloxone were submitted or required for this application.

5.2 Toxicokinetics

No new toxicokinetics studies with intranasal naloxone were submitted or required for this application.

6 General Toxicology

No new general toxicology studies with intranasal naloxone were submitted or required for this application. The Applicant is relying upon the Agency's finding of safety for NDA 016636 (NARCAN [Naloxone HCl] Injection).

Note, during the pre-IND meeting with the Applicant (IND134611, Type B meeting, December 20, 2018) no new nonclinical local tolerance studies were requested by the Division because no novel excipients were included in the to-be-marketed formulation and adequate monitoring of local tolerance in the clinical studies was conducted[11]. Further, NARCAN (Naloxone HCl) Nasal Spray (NDA 208411), another intranasal product with a comparable maximum daily dose of naloxone HCl, was approved for prescription use in 2015. Since its approval, an abundance of clinical safety information is available to support the local safety of the drug product.

A cursory review of the intranasal nonclinical toxicity study submitted to IND134611 (Study Title: *A 1-and 7-Day Intranasal Safety Study in Male Rats with Naloxone HCl Dihydrate;* see Tables 10 and 11*)* was also performed. There were no test article-related findings reported in that study.

7 Genetic Toxicology

No new genetic toxicology studies with intranasal naloxone were submitted or required for this application. The Applicant is relying upon the Agency's finding of safety for NDA 016636 (NARCAN [Naloxone HCl] Injection).

[11] PIND 134611, Type B meeting with the Applicant, Meeting Minutes 12/20/18, Reference ID 4363712

An excerpt from the Rx label for NARCAN (Naloxone HCl) Injection regarding genetic toxicity is provided below:

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

8 Carcinogenicity

No new carcinogenicity studies with intranasal naloxone were submitted. The Applicant is relying upon the Agency's finding of safety for NDA 016636 (NARCAN [Naloxone HCl] Injection). An excerpt from the Rx label for NARCAN (Naloxone HCl) Injection regarding carcinogenicity follows: "Studies in animals to assess the carcinogenic potential of NARCAN have not been conducted."

9 Reproductive and Developmental Toxicology

> No new reproductive and developmental toxicology (DART) studies with intranasal naloxone were submitted or required for this application. The Applicant is relying upon the Agency's finding of safety for NDA 016636 (NARCAN [Naloxone HCl] Injection). An excerpt from the Rx label for NARCAN (Naloxone HCl) Injection regarding DART follows: "Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to NARCAN."

Note, the exposure margin for the reproduction studies referenced above from the Rx label for NARCAN (Naloxone HCl) Injection relied upon a clinical MDD of 10 mg/day. The MDD of the proposed intranasal drug product is only 6 mg/day. Therefore, when relying upon a clinical MDD of 6 mg/day, the exposure margin for the reproduction studies conducted in mice and rats is approximately 8-times and 16-times the dose of a 50 kg human, respectively. Further, data from fertility and embryonic development, embryo-fetal development, and pre- and post-natal developmental reproduction studies in rats and an embryo-fetal study in mice were previously submitted to support NDA 16636 NARCAN (Naloxone HCl) Injection. These studies were previously reviewed (see nonclinical review by Dr. Edward Tocus, dated May 12, 1969) and are summarized in the P/T review for the original prescription NARCAN (Naloxone HCl) Nasal Spray (NDA 208411) [12].

[12] NDA Pharmacology and Toxicology Review, primary reviewer: Newton Woo, PhD. 11/2/15. Reference ID: 3841831

10 Integrated Summary and Safety Evaluation

The Applicant, Harm Reduction Therapeutics Inc, has submitted a 505(b)(2) NDA for RiVive Nasal Spray (naloxone hydrochloride 3 mg/0.1 mL). 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 NDA, and none was required. The Applicant is relying upon the Agency's finding of safety for NDA 016636 (NARCAN [Naloxone HCl] Injection).

From the nonclinical perspective, this NDA application is approvable.

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/

CHIBUEZE A IHUNNAH
05/15/2023 12:16:39 PM

DONALD C THOMPSON
05/15/2023 02:41:54 PM
I concur.