Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

# CLINICAL/CROSS-DISCIPLINE TEAM LEADER/DIVISION DIRECTOR REVIEW

| | |
|---|---|
| Application Type | Supplemental New Drug Application (sNDA) |
| Application Number(s) | 212045 S-005 |
| Priority or Standard | Standard |
| Date | Refer to signature sheet |
| PDUFA Goal Date | August 25, 2025 |
| Division/Office | Division of Anesthesia, Addiction Medicine, and Pain Medicine/Office of Neuroscience |
| Reviewer Name(s) | Zachary Dezman, MD, MS (Primary Clinical Reviewer)<br>Tina Doshi, MD, MHS (Acting Cross-Discipline Team Leader/Associate Director for Therapeutic Review)<br>Leah Crisafi, MD, FASA (Division Director) |
| Established/Proper Name | Naloxone hydrochloride |
| (Proposed) Trade Name | Kloxxado |
| Applicant | Hikma Pharmaceuticals USA Inc |
| Dosage Form(s) | Intranasal spray |
| Applicant Proposed Dosing Regimen(s) | 4 mg of naloxone hydrochloride (equivalent to 3.6 mg naloxone) or 8 mg of naloxone hydrochloride (equivalent to 7.2 mg naloxone) in 0.1 mL of spray (intranasal). [1] |
| Applicant Proposed Indication(s)/Population(s) | Kloxxado is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, for adult and pediatric patients.<br>Kloxxado is intended for immediate administration as emergency therapy in settings where opioids may be present.<br>Kloxxado is not a substitute for emergency medical care. |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) (if applicable) | As above |

REVIEW TEAM

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## Glossary

| | |
|---|---|
| AE | adverse event |
| BRF | Benefit Risk Framework |
| CDER | Center for Drug Evaluation and Research |
| CMC | chemistry, manufacturing, and controls |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| FDA | Food and Drug Administration |
| GCP | good clinical practice |
| GRMP | good review management practice |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NDA | new drug application |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Key Regulatory History

Kloxxado (intranasal naloxone, 8 mg) was approved on April 30, 2021, for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, for adult and pediatric patients. (b) (4)

In March 2023, (b) (4) Narcan Nasal Spray (4 mg, IN, NDA 208411), the reference product for this NDA, was approved for nonprescription (previously referred to as over-the-counter [OTC]) use. (b) (4)

(b) (4) The sole study supporting approval is Study NAL-NS0521/45, a comparative bioavailability (b) (4) This review will emphasize the key interim scientific data.

## 1.2. Product Introduction

Naloxone is a nonselective opioid receptor antagonist, with greatest affinity for the mu opioid receptor. Similar to nalmefene and naltrexone, naloxone antagonizes opioid effects by competing for the mu, kappa, and sigma opioid receptor sites in the central nervous system (CNS).[11] The Applicant seeks approval for a drug-device product containing 4 mg of naloxone hydrochloride for the treatment of opioid overdose. The device component utilizes the same (b) (4) nasal spray device used in the parent NDA (Kloxxado [NDA 212045], see Figure 1, below) and several other products approved for similar indications (Narcan [NDA 208411], RIVIVE (b) (4) REXTOVY NDA 208969], Rezenopy NDA 215487], and OPVEE [NDA 217470]).[2, 3, 12-14] The active substance of the proposed product also contains (b) (4) propylene glycol and 24.305% ethanol, (b) (4) As shown in Section 4.5 Clinical Pharmacology, (b) (4) . The mean naloxone $C_{max}$ with the HIKMA 4 mg product detailed in this submission are nearly twice that of the nonprescription Narcan 4 mg product. Therefore, despite containing the same nominal dose as Narcan nasal spray, we consider the HIKMA 4

mg product a" high-exposure" product, more consistent with the HIKMA 8 mg nasal spray and the ZIMHI 5 mg prefilled syringe.

As with other naloxone products (e.g., listed above), the proposed product is intended to be sold in pairs, which allows the administrator to give an initial dose and a repeat dose in case of device malfunction or if the patient does not respond by the time emergency providers arrive.


Figure 1. The Kloxxado [NDA 214045] 8mg product, which uses the same (b) (4) delivery device as the proposed product. [15]

The proposed indication for this efficacy supplemental New Drug Application (sNDA) is [16]:

1. Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
2. Immediate administration as emergency therapy in settings where opioids may be present.

These indications are identical to those for the previously approved Kloxxado 8 mg product.

## 1.3. Conclusions on the Substantial Evidence of Effectiveness

The comparative bioavailability study (b) (4) Dr. Silvana Borges (DAAP Deputy Division Director) wrote:

> The efficacy of Naloxone NS 4 mg was evaluated in one PK study comparing the systemic exposure to naloxone following the administration of Naloxone NS 4 mg, Narcan nasal spray 4 mg (NDA 208411) and Kloxxado naloxone nasal spray 8 mg (NDA 212045). In this PK study, naloxone NS 4 mg demonstrated higher plasma concentrations at the early absorption phase, greater $C_{max}$, greater $AUC_{0-t}$ and $AUC_{0-inf}$ than Narcan and lower $C_{max}$, $AUC_{0-t}$, $AUC_{0-inf}$ than Kloxxado. Therefore, naloxone NS 4 mg has demonstrated naloxone systemic exposure between that of Narcan and Kloxxado, supporting the Applicant's proposed reliance on efficacy findings of Narcan and systemic safety findings of Kloxxado.

## 1.4. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Naloxone is a nonselective opioid receptor antagonist with greatest affinity for the mu-opioid receptor. It was developed and approved to reverse life-threatening opioid overdose and prevent hypoxia associated with injury and death (NDA 016636). Many approved, currently marketed opioid reversal agents utilize naloxone, although more recently several opioid reversal agents have been approved that utilize nalmefene (see Section 2.2 Analysis Current Treatment Options). Kloxxado is a drug-device combination that delivers 100 µL of a solution containing 4 mg of naloxone hydrochloride, administered using the (b) (4) nasal spray device, intended for use in community settings in patients of all ages. The Applicant has fulfilled the efficacy requirements for this indication, the safety profile is consistent with other approved products in the class, and the Applicant has adequately responded to the Agency's prior concerns (b) (4)

Opioid overdose is the cause of more than 1,600,000 emergency department visits and approximately three-quarters of the 100,000 overdose deaths occurring in the United States annually.[18-20] Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that can lead to significant morbidity and mortality due to hypoxic injury, acidosis, and cardiac arrest.[21] Death due to overdose from most opioids may be preventable with the immediate administration of an opioid antagonist such as naloxone, in combination with basic first aid and professional medical care (e.g., emergency medical services, emergency department care). Opioid overdose is a serious risk for many, including persons who abuse opioids (e.g., heroin, illicit fentanyl, and diverted prescription opioids), close contacts of such persons, patients prescribed opioids for acute (e.g., surgeries, trauma) or chronic pain (e.g., cancer), patients prescribed opioids for the treatment of opioid use disorder, and persons who may be exposed accidentally (e.g., children living with such individuals).[22-26] Therefore, products indicated for the emergency treatment for opioid overdose are ideally safe, effective, and easy-to-use for all ages, populations, and skill levels.[7]

The efficacy of the proposed product is supported by a scientific bridge using a pharmacokinetic study (NAL-NS0521/45) in healthy volunteers, which demonstrated that the proposed product generates plasma naloxone levels within the range of those produced by the approved reference products (NDA 208411 and parent NDA 212045). The primary risks of naloxone exposure are precipitated opioid withdrawal in the opioid-dependent patient population and cardiovascular risks of rapid opioid reversal.[27, 28] Common symptoms of opioid withdrawal include agitation, anxiety, muscle aches, rhinorrhea, diaphoresis, diarrhea, vomiting, and pruritis.[29] In neonates exposed to opioids before birth, neonatal opioid withdrawal syndrome may be life-threatening.[30] In opioid-dependent persons, the symptoms of opioid withdrawal may be so severe that patients and advocates have cited a fear of withdrawal as a reason to use substances alone and to not carry naloxone.[31] Beyond the risk of precipitated withdrawal, abrupt postoperative reversal of opioids has been shown to lead to adverse cardiovascular events such as

hypotension, hypertension, ventricular tachycardia, and ventricular fibrillation. Pulmonary edema is a rare, but potentially life-threatening complication of naloxone administration that appears to be dose-dependent.[32, 33]

While there is sufficient evidence of safety and efficacy of the proposed product for the proposed indication, its potential approval highlights underlying concerns regarding appropriate selection of naloxone product(s) for a given patient. Beyond their pharmacokinetic study (NAL-NS0521/45), the Applicant has not provided evidence demonstrating any differences in safety or efficacy between their approved 8 mg product (parent NDA 212045) and the proposed 4 mg product. Similarly, while there is pharmacokinetic evidence of increased naloxone exposure with the Kloxxado 4 mg product compared to the reference naloxone 4 mg nasal sprays, it remains unclear the extent to which this finding affects the comparative safety and/or efficacy of the Kloxxado product. Lastly, no data have been submitted regarding the safety or efficacy of either Kloxxado product in opioid-dependent persons.

The theoretical differences in benefit-risk profile and the paucity of data supporting clinically meaningful differences among naloxone nasal spray products (particularly Kloxxado 8 mg versus 4 mg, and OTC Narcan 4 mg versus prescription Kloxxado 4 mg) present a challenge for patients and prescribers trying to choose the most appropriate product. The Division has therefore required modification to the Applicant's proposed labeling to reflect what is currently known regarding the comparative efficacy of differing nominal doses of naloxone and the risk of precipitated withdrawal in opioid-dependent persons. Furthermore, the clinical review team recommended two post-marketing requirements (PMRs) to address the remaining knowledge gaps: 1) conduct a safety study in opioid-dependent persons, and 2) conduct a study comparing the proposed 4 mg product and the parent 8 mg product, showing differences in efficacy or safety (or both). However, given that the currently proposed product represents a *lower* dose and exposure compared to the approved parent product, it does not present increased concerns regarding the product's safety, efficacy, or optimal use. Therefore, a PMR will not be a condition of approval for this submission. While the Agency acknowledges that data from the recommended studies would better inform the respective benefit-risk profiles for the two products under this NDA, the Agency will continue to consider and pursue the various regulatory and non-regulatory options to guide regulation of these products and opioid reversal agents more broadly.

The sNDA 212045/S-005 supports the approval of the proposed product for the proposed indication.

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Around 80% of the 106,699 drug overdose deaths in the United States in 2021 involved an opioid.[34]<br>• On average, 230 Americans die every day from opioid overdoses.[34]<br>• Opioid overdose affects all ages, including elderly and pediatric patients.[35, 36] | Opioid overdose occurs in a broad patient population, including both opioid-dependent and non-opioid-dependent persons. Opioid overdose and death continue to be a public health crisis and a leading cause of death in the US. |
| Current Treatment Options | • There is a wide selection of currently approved and available products containing naloxone and nalmefene, including those that are intended for community use.<br>• Naloxone can be administered through the intravenous (IV), intranasal (IN), and intramuscular (IM) routes.[37]<br>• Narcan and RIVIVE, both 4 mg IN sprays, are considered safe and effective for non-prescription use.[38, 39]<br>• Some overdoses have required multiple administrations of standard doses of naloxone.[40-44] It is not known whether these represent failures of the products approved for use in the community, the increasing prevalence of more potent synthetic opioids (e.g., fentanyl and analogs), or co-ingestions of intoxicants without mu-opioid receptor activity (e.g., xylazine). | The broad array of opioid reversal products, including various doses and routes of administration, facilitates increased availability and use of naloxone to rescue patients. There are many FDA-approved treatment options available to treat opioid overdose, some of which have been approved for non-prescription use.<br><br>While naloxone can reverse the acute opioid intoxication of a patient, receiving naloxone is not a permanent solution for opioid abuse, misuse, and addiction. |
| Benefit | • The efficacy of this product for community use is supported by a scientific bridge between the proposed product (Kloxxado, 4 mg naloxone hydrochloride delivered in 100 µL via IN spray) and the reference products, Narcan 4 mg naloxone hydrochloride (NDA 208411) and the parent Kloxxado 8 mg naloxone hydrochloride (NDA 212045), established through the PK study NAL-NS0521/45.<br>• There are no clinical efficacy data submitted in support of the proposed product to help assess its efficacy in treating overdoses | The Applicant provided literature and PK data to support the effectiveness of the proposed product for the proposed indication. The supplement contains no evidence that this product will result in improved outcomes in reversing specifically synthetic opioids or opioid overdose in general compared to other approved products. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | from synthetic opioids.<br>• There are no comparative efficacy data between the proposed product and other approved opioid reversal products for community use. | |
| Risk and Risk Management | • Naloxone administration may cause withdrawal symptoms in opioid-dependent individuals. Precipitated withdrawal may be severe and if left untreated, it can lead to dehydration, electrolyte abnormalities, and renal failure. These products are intended to save the lives of persons who use illicit opioids, but the same population may be less accepting and less likely to use products that frequently precipitate withdrawal.<br>• The likelihood of precipitated withdrawal is increased with higher exposure to naloxone, but the exact relationship between naloxone exposure and precipitated withdrawal in opioid-dependent persons is not well-characterized.<br>• There are reports of patients suffering from noncardiogenic pulmonary edema after receiving naloxone.[17]<br>• Proposed product labeling includes language about the serious risks of precipitating acute opioid withdrawal. There are no comparative safety data between this product and other currently available reversal products to inform prescribing decisions. | The Applicant has not provided data to describe the frequency of precipitated opioid withdrawal in opioid-dependent patients who are treated with the product. Based on evidence from the literature and other Applicants/NDAs, we would expect the current proposed product to have comparable safety to existing opioid reversal products. The risk can be mitigated through labeling.<br><br>Approval of this product would provide an additional approved opioid reversal product, but without comparative safety data to inform prescriber selection from among many similar products. A study to inform differences in safety between products could be informative to prescribers., |

## 1.5. Patient Experience Data

Several sources of patient experience data that relate to the concern of precipitated withdrawal were used to inform this review (Table 2). A Patient-Focused Drug Development Meeting relating to Opioid Use Disorder (OUD) was held on April 17th, 2018. The meeting featured the experience of patients with OUD, guided by moderators. From the summary report:[45]

> Page 5: "Participants described 'being a prisoner' to opioid withdrawals often accompanied by nausea, vomiting, and uncontrollable muscle spasms. Participants also offered insight on opioid 'cravings,' or desire to use... Participants also stressed that cravings may last well beyond acute withdrawal and can be triggered unpredictably."
>
> Page 7: "Meeting participants referred to the symptoms of opioid withdrawal as feeling 'drug sick.' Throughout the large-group discussion participants highlighted avoiding the feeling of being 'drug sick' during opioid withdrawals often hindered their recovery. One participant shared, 'Always the withdrawals drove me back to opioids.' Another participant described the 'unsurmountable' challenges of opioid withdrawal stating, 'Opioid use sort of drove my daily activities as I would be drug sick if I didn't [obtain opioids].' During meeting discussion individuals described opioid withdrawal in vivid detail in the statements below:
> - 'The feeling of these bugs like crawling underneath my skin and chewing their way through my body.'
> - 'Skin crawls where you can't lay still…your body just jerks. You feel like a cat on a hot tin roof.'"

Public comments submitted to the docket described a similar impact of OUD, opioid dependence, and opioid withdrawal on individuals, consistent with those discussed at the meeting.

An FDA Reagan-Udall meeting was held March 8-9, 2023, regarding the current management of opioid overdose.[31] Patient advocates and addiction medicine specialists contributing to the meeting requested greater involvement of persons who use drugs in the development of opioid reversal products, as that community would be the primary users and beneficiaries of these products. The patient advocates recognized that opioid overdose is life-threatening and a greater immediate risk than precipitated opioid withdrawal. However, there remains a substantial public health concern regarding the risk of decreased acceptance of opioid-overdose reversal products by persons who use drugs if the only available products precipitate opioid withdrawal.

On, March 19, 2024, an independent healthcare research firm convened the Compassionate Overdose Response Summit, in which experts, advocates, and patients discussed current trends in opioid overdose care, with a focus on naloxone administration.[46] As a part of the summary presentation and panel, Joy Rucker, founder of the Texas Harm Reduction Alliance and the

Black Harm Reduction Network, shared her experience of being revived from several opioid overdoses: "When you have withdrawal symptoms, you want to die. You feel like you're going to die. If it's not necessary to bring someone there, don't. We must get someone breathing to save their life." Ms. Rucker's comments re-emphasized the continued recognition of withdrawal as a serious concern among patients and are representative of the careful balance between life-saving benefit and potential patient harm that must be made with any decision to administer an opioid reversal agent.

These public meetings have identified several key steps that the Agency could take to improve the experience of patients being revived by opioid reversal products and mitigate the potential harms of naloxone administration and precipitated opioid withdrawal.[31, 45, 46] Specific recommendations related to this application include:

- Involve persons who use opioids in decisions regarding the research, development, selection, and distribution of opioid overdose reversal products.
- Support availability of a wide array of opioid reversal products, covering multiple routes of administration appropriate for victims of opioid overdose (IM, SC, IV, IN, etc.).
- Consider adjustable devices that can provide a range of doses and/or multiple doses.
- Note that many patients, clinical experts, and advocates consider longer-acting antagonists (i.e., eight to 12 hours) and stronger dose alternatives than the standard 0.4 mg intramuscular and >4 mg intranasal to be unnecessary in the current landscape of opioid overdoses.
- Consider and communicate the risk and duration of withdrawal associated with higher dose and long-acting opioid antagonists.

Table 1. Patient Experience Data Relevant to this Application

| ☐ | The patient experience data that was submitted as part of the application include: | | Section where discussed, if applicable |
|---|---|---|---|
| | ☐ | Clinical outcome assessment (COA) data, such as | |
| | ☐ | ☐ Patient reported outcome (PRO) | |
| | ☐ | ☐ Observer reported outcome (ObsRO) | |
| | ☐ | ☐ Clinician reported outcome (ClinRO) | |
| | ☐ | ☐ Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | |
| | ☐ | Observational survey studies designed to capture patient experience data | |
| | ☐ | Natural history studies | |

| | | | | |
|---|---|---|---|---|
| | ☐ | | Patient preference studies (e.g., submitted studies or scientific publications) | |
| | ☐ | | Other: (Please specify) | |
| ☒ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | ☒ | Input informed from participation in meetings with patient stakeholders | Section 1.4 |
| | | ☒ | Patient-focused drug development or other stakeholder meeting summary reports | Section 1.4 |
| | | ☐ | Observational survey studies designed to capture patient experience data | Section 1.4 |
| | | ☐ | Other: (Please specify) | |
| ☐ | Patient experience data was not submitted as part of this application. | | | |

# 2. Therapeutic Context

## 2.1. Analysis of Condition

Opioid overdose is a syndrome of decreased awareness, bradycardia, and bradypnea resulting from exposure to opioids. Untreated, opioid overdose can lead to life-threatening respiratory failure, permanent hypoxic injury, and death., Most opioid overdoses in the United States are due to illicit opioids. However, they may also occur due to medication errors, drug-drug interactions, or other concomitant illnesses in patients being treated with opioids for pain. They may also occur in children and infants due to unintentional exposure.[47] In 2021, there were 106,699 such drug overdose deaths in the United States, and approximately 80% of these deaths involved an opioid.[34]

Two key epidemiologic trends in opioid overdose deaths are relevant to this supplement. First, the proportion of opioid-related overdoses and deaths associated with opioid prescriptions has declined. Fentanyl and fentanyl analogs manufactured overseas had begun to appear on the American illicit drug market in 2015 in different forms, including pressed into pills and sold as OxyContin [48], or sold as a powder and mixed with, or passed off as, heroin.[49] The potency and uneven quality of street preparations of illicit fentanyl led to rapid increases in fatal and non-fatal opioid overdoses,[50] leading to the largest drop in US life expectancy before the COVID pandemic in 2020.[51] Much of the illicit opioids sold in the US now contain fentanyl or are mostly fentanyl, and nearly all opioid fatal and nonfatal opioid overdoses involve fentanyl.[52] Today, fentanyl is increasingly being mixed with non-opioid substances, including stimulants (e.g., cocaine, methamphetamine) or sedatives (e.g., xylazine, nitazenes).[53-55]

Second, although opioid overdose deaths remain high, there has been an overall decrease (21.7%) in overdose deaths in the US over the last year (Figure 2 [56]). This trend has been

attributed to several factors: a decrease in the lethality of the substances sold on the drug market, concomitant increases in xylazine and methamphetamine and a decrease in fentanyl associated with drug overdoses,[57, 58] users shifting towards less dangerous forms of use,[59] improved access to substance abuse treatment programs, and saturation of the market for overdose reversal products.[5, 6, 60, 61]

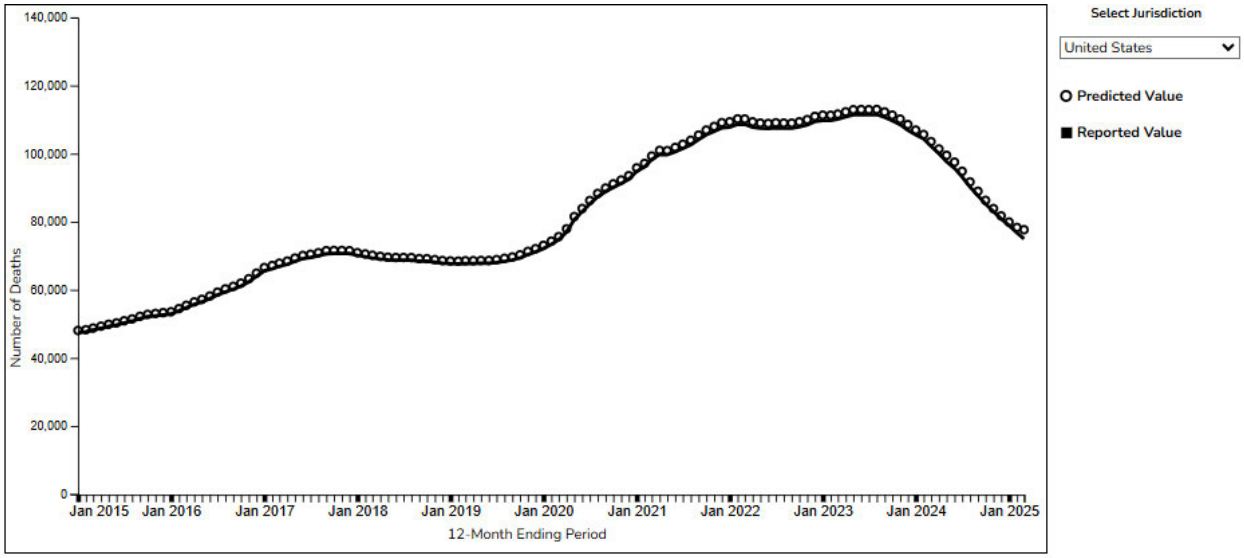



Figure 2. Twelve Month-ending Provisional Number and Percent Change of Drug Overdose Deaths (Based on data available from August 25th, 2025, from CDC National Vital Statistics System).

## 2.2. Analysis of Current Treatment Options

There are a range of products indicated for opioid overdose in community settings (Table 2). Note there are also naloxone-containing products intended to treat opioid exposure or to prevent opioid overdose in military personnel exposed to chemical weapons or first responders exposed to chemical hazards, but they are not relevant to the current supplement.

Table 2. Summary of Naloxone and Nalmefene Products Relevant to Proposed Indication

| Product (s) Name | Year of Approval | Route and Frequency of Administration | Efficacy Information | Other Comments |
|---|---|---|---|---|
| Approved treatments containing naloxone | | | | |
| Narcan (NDA 16636, many generics [ANDA] available) | 1971 | Injection for IV, IM, SC. Available concentrations: 0.02 mg/mL, 0.4 mg/mL, and 1 mg/mL | Onset of action is apparent within two minutes | Approved for use in entire pediatric range. |
| Narcan (NDA 208411) | 2015 | 4 mg nasal spray | Onset of action is apparent within two minutes | Non-prescription as of 3/2023 |
| Kloxxado (parent | 2021 | 8 mg nasal spray | Onset of action is | Prescription |

| | | | | |
|---|---|---|---|---|
| NDA 212045) | | | apparent within two minutes | |
| Zimhi NDA 212854 | 2021 | 5 mg prefilled syringe IM/SC | | Prescription |
| Rivive (NDA 217722) | 2023 | 3 mg nasal spray | Onset of action is apparent within two minutes | Non-prescription as of 7/2023 |
| Rextovy (NDA 208969) | 2023 | 4 mg nasal spray | Onset of action is apparent within two minutes | Applying for non-prescription status |
| Rezenopy (NDA 215487) | 2024 | 10 mg nasal spray | Onset of action is apparent within two minutes | Prescription |
| Approved treatments containing nalmefene | | | | |
| Revex (NDA 20459, generics available) [62-64] | 1995 | IV:0.5 to 2.0 mg<br>IM/SC: I mg | IV: within 2 to 5 minutes<br>IM/SC: within 5-15 minutes | Discontinued in 2014 not for safety or efficacy reasons. Safety and efficacy in pediatric patients has not been established. |
| Opvee (NDA 217470)[13] | 2023 | 2.7 mg nasal spray | IN: within 5 minutes | Approved as prescription for 12 y/o and older |
| Zurnai (NDA 218590) | 2024 | 1.5 mg autoinjector IM/SC | IM/SC: within 5 minutes | Approved as prescription for 12 y/o and older |
| Approved but Currently Not Marketed | | | | |
| Evzio (NDA 205787) | 2014 | 0.4 mg autoinjector IM/SC | | Withdrawn from market [65] |
| Evzio (NDA 209862) | 2016 | 2 mg autoinjector IM/ SC | | Withdrawn from market [65] |
| Narcan (NDA 208411) | 2017 | 2 mg nasal spray | Onset of action is apparent within two minutes | Never marketed |

IV = intravenous; IM = intramuscular; SC = subcutaneous

Naloxone (Narcan, NDA 16636) [1] was approved in April 1971 and is available for subcutaneous, intramuscular, and intravenous use for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids. Narcan is also indicated for the diagnosis of suspected or known acute opioid overdosage. Naloxone (see Figure 3) antagonizes opioid effects by competing for the mu, kappa, and sigma opioid receptor sites in the CNS. It can effectively and rapidly reverse opioid overdose symptoms if given shortly (<2-3 minutes) after the development of symptoms.[66]

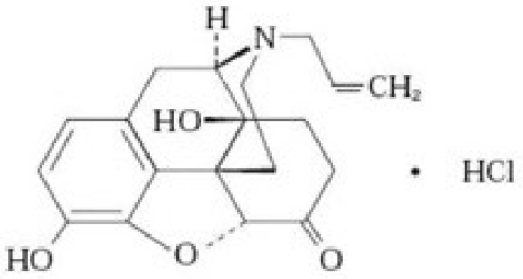


Figure 3. Chemical structure of naloxone hydrochloride

When naloxone is administered IV, the onset of action is generally apparent within 2 minutes; the onset of action is slightly less rapid when it is administered by SC or IM injection or intranasally (IN). Naloxone product labels recommend initial doses of 0.4 mg to 2 mg naloxone hydrochloride by the IM or IV route of administration, respectively, followed by repeat doses up to a total dose of 10 mg. Naloxone nasal sprays are available in fixed-dose presentations ranging from 3 mg to 10 mg. There is no maximum dose of naloxone; a practitioner is cautioned to consider alternative causes for a patient's presentation once 10 mg has been administered.

Though naloxone administration generally has only mild effects in opioid-naïve persons, it can cause opioid withdrawal in persons with opioid dependence. Opioid withdrawal is characterized by generalized pain or achiness, chills, nausea, vomiting, diarrhea, diaphoresis, insomnia, tremors, anxiety, restlessness, piloerection, yawning, and mydriasis. The risk of a patient with OUD developing opioid withdrawal after reversal is dose-dependent.[8] Uncomplicated opioid withdrawal is uncomfortable but is not life-threatening for most adults. However, if untreated, it can precipitate complications like dehydration, kidney injury, and electrolyte imbalances. In children and infants, opioid withdrawal can lead to life-threatening seizures.[70] Among people who use drugs, the risk of withdrawal has been identified as one of the largest barriers to decreasing substance use.[29, 71]

Noncardiogenic pulmonary edema is a potentially life-threatening complication estimated to occur in 1%-2% of patients receiving naloxone.[32, 72, 73] While the development of pulmonary edema after receiving naloxone is more commonly reported in patients suffering from illicit opioid overdose, it has also been reported among patients without a history of opioid use who received postoperative opioids.[74-77] The pathophysiological mechanism of noncardiogenic pulmonary edema is thought to be a catecholamine surge associated with the rapid reversal of opioid agonist effects. The risk of pulmonary edema after opioid overdose reversal appears to be correlated with increased naloxone dose [32, 33] and not specific to naloxone, as it has also been reported in patients receiving nalmefene.[78]

As with the parent product of the current submission, Applicants submitting marketing applications for opioid reversal agents have justified high-dose/high-exposure naloxone products by citing the rising prevalence of high-potency opioids like fentanyl and fentanyl analogs. Naloxone was approved long before the advent of illicit fentanyl, and there has not been a prospective trial of naloxone to treat opioid overdose due to illicit fentanyl exposure. Thus, although the mechanism of naloxone reversal is applicable to all traditional opioids, it is not clear what constitutes the most appropriate dose of naloxone in the current era of fentanyl and fentanyl analogs. However, emerging evidence from retrospective state- and nation-wide data sources suggest most opioid overdose patients who are treated in time do not require high doses of naloxone, regardless of opioid source.[9, 27, 40, 43, 79-84]

Notably, the United States is unique in its approvals of high-exposure naloxone products. Arne Skulberg, MD, PhD, a Norwegian researcher who conducted one of the few modern trials of

naloxone in the prehospital environment,[85] stated, "What you [the U.S.] describe as low-dose, the 4 mg ones would in most European countries be considered a high dose, and when you start talking about 8 mg naloxone, [Europeans] are shaking our heads and can't really understand it."[46] In December 2024, Health Canada consulted the FDA to discuss how the FDA approaches naloxone-containing products. They noted that Canadian patients had voiced concerns like those of American patients (see Section 1.5), and there remains a knowledge gap regarding the relative safety and efficacy of high-exposure naloxone products versus lower-exposure products in various clinical scenarios. Health Canada specifically asked whether the Agency had any safety concerns regarding products containing high doses of naloxone, and whether those concerns played a role in how the Agency decides which products are reviewed and approved as prescription or non-prescription.

Although the observed nationwide decrease in fatal opioid overdoses (see Figure 3 and Section 2.1) may be at least partially attributable to the increased overall availability of naloxone products, [5, 6, 60, 61] the contribution of high-exposure products to this trend is likely low. The Office of Surveillance and Epidemiology (OSE) provided an accounting of the number of purchases of naloxone products distributed, stratified by product, year, data source, and purchaser.[86] Naloxone distribution doubled between 2021 and 2023 (Figure 4). Although over (b) (4) were sold to traditional healthcare settings in 2023 (like 2021), the distribution of the remaining (b) (4) units is unknown. These naloxone products were likely distributed to non-traditional settings, such as State Health Departments, harm reduction programs, and law enforcement (Figure 5). The increased distribution of naloxone over this time coincides with the observed decrease in overdose deaths (Figure 2). Importantly, only a small portion of the increased sales came from high-exposure (8 mg) prescription products (Figures 4 and 5); the preponderance of sales came from OTC and prescription naloxone 4 mg nasal sprays.


**Figure 4.** (left) Applicant Distribution Data, 2021 and 2023, and 2023.

**Figure 5.** (right) Applicant Submitted Data Versus IQVIA Data, 2023

Notably, Alaskans received more doses of the high-exposure 8 mg product than any state by a large margin (Figure 6). If high-exposure products had a significant impact on fatal overdoses,

one would expect to see a decrease in the fatal overdose rate in Alaska in 2023. While Alaska did have a decline in opioid overdose deaths, it did not occur until July 2024 (Figure 7), a year later than the US as a whole (Figure 2). Dr. Zachary Dezman spoke with the Alaskan State Health Department regarding these observations. The Health Department did not have any data, anecdotal or otherwise, to support any safety or efficacy differences between naloxone-containing products. The 8 mg high-exposure products had been purchased in such large quantities due to a one-time price break by the Applicant; the Alaskan State Health Department has since switched to the 4 mg Narcan product, as it became the cheapest option.


**Figure 6.** Differential Distribution of High Dose Naloxone, Sales to Non-Retail Settings, Sept 2021-November 2024

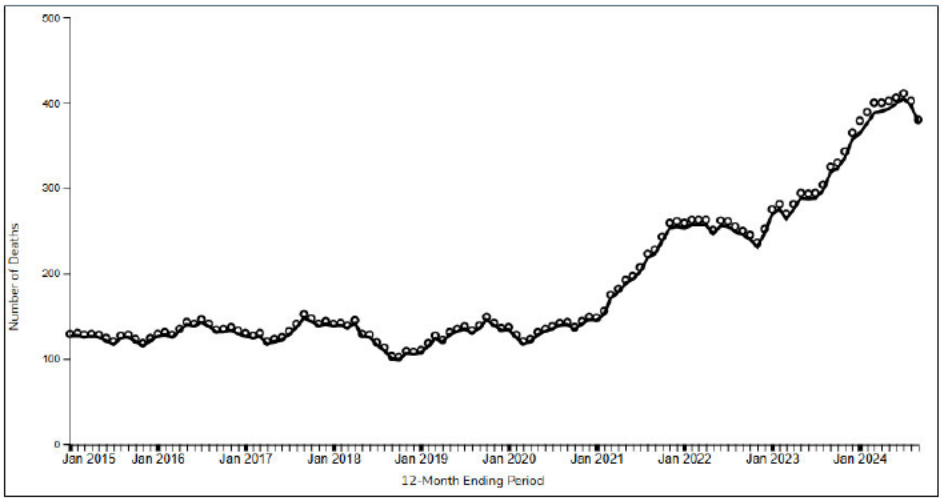



**Figure 7.** 12 Month-ending Provisional Counts of Drug Overdose Deaths: Alaska [Source: CDC National Vital Statistics System, Provisional Drug Overdose Death Counts][87]

The other drug indicated for the treatment of opioid overdose is nalmefene. Injectable nalmefene (Revex) was approved in 1995 (NDA 020459)[62] and was removed from the market for business reasons in 2008. The FDA determined it was not discontinued or withdrawn for

reasons of efficacy or safety in 2017. Generic nalmefene was reintroduced to the market in 2022,[63, 64] and it is currently available as a sterile solution for IV, IM and SC administration.

Two community-use drug-device products for the emergency treatment of opioid overdose have been approved in recent years:

- Opvee (NDA 217470), a drug-device combination nasal spray delivering 2.7 mg of nalmefene hydrochloride via the (b) (4) device, was approved in 2023,[13] and
- Zurnai (NDA 218590), an autoinjector delivering 1.5 mg nalmefene hydrochloride, was approved for the treatment of opioid overdose in 2024.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

The first product approved to address the risk of opioid overdose in a community setting was EVZIO (naloxone hydrochloride injection), approved on April 3, 2014. Evzio (NDA 205787) is an autoinjector that delivers 0.4 mg of naloxone in 0.4 mL to the subcutaneous or intramuscular space. A higher-dose version, Evzio 2 mg (NDA 209862) was approved on October 19, 2016. Both products have since been removed from the market by the Applicant for reasons other than safety or efficacy. Narcan nasal spray (NDA 208411) was approved on November 18, 2015, and consists of a single-dose device of 4 mg naloxone in 0.1 ml. (b) (4) The Narcan 4 mg nasal spray product was later approved for non-prescription use March 2023 (see DNPD1 review for further details). Rextovy (NDA 208969), a 4 mg IN product, was approved as a prescription in March 2023, (b) (4). Zimhi, a syringe pre-filled with 5 mg of naloxone for IM/SC injection, was approved in 2021 (NDA 212854). Kloxxado is an 8 mg nasal spray that was approved in 2021 (NDA 212045) and has subsequently been purchased by the current Applicant. Another drug-device product using naloxone and the (b) (4) delivery device, Rivive 3mg nasal spray (NDA 217722), was approved as a direct-to-nonprescription product in July 2023 (see DNPD1 review for further details). Most recently, Rezenopy, a 10 mg nasal naloxone spray, was approved in April 2024.

At the time of Rezenopy's review, a report was published in the Centers for Disease Control and Prevention (CDC) *Morbidity and Mortality World Report (MMWR)*, providing preliminary evidence of the hazards of high-exposure products for those persons who use drugs in the prehospital care environment.[27] Note this review intentionally uses the term "exposure" at times instead of "dose". Because of different excipients and routes of administration, the naloxone exposure from a given product (i.e., the serum level of drug after the product is administered) is not directly related to the product's nominal dose. Allowing for the limitations of cross-study comparisons, data submitted to the FDA suggest some approved naloxone products with higher nominal doses produce lower exposures than other products, and vice-versa. The data provided to the FDA are insufficient to determine whether providers and

patients can identify distinctions between products, or whether these variants in exposure lead to clinically significant differences in outcomes between products.

During the NDA review of Rezenopy, the reviewer requested a post-marketing requirement be made for the Applicants for the currently- and soon-to-be-approved high-exposure products: Kloxxado, ZIMHI, and Rezenopy. The decision was made to not pursue a PMR at that time, given the ongoing severity and lethality of the opioid crisis supporting the need for greater availability of naloxone products and the preliminary nature of the CDC *MMWR* report.

As a part of its mission to improve the health of the American public, the FDA has focused on making opioid reversal products available to improve access and prevent deaths. However, there is admitted absence of clinical trial data substantiating the most safe and effective dose of naloxone in the era of fentanyl, especially for those patients who use drugs or have opioid dependency. Nonetheless, patients, advocates, international experts, and counterpart governmental agencies all appear to share concerns that the trend towards high-dose/high-exposure opioid reversal products may be harmful to patients without an attendant improvement in efficacy.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

Hikma submitted New Drug Application (NDA) 212045 to DAAP in April 2019 for a drug-device product containing a solution of 8 mg naloxone hydrochloride, 20% ethanol (by weight), and (b) (4) propylene glycol, to be administered intranasally via a single-use device from (b) (4). The application was approved via the 505(b)(2) pathway in April 2021 under the tradename Kloxxado with the following indications:

> "Kloxxado is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, for adult and pediatric patients.
>
> Kloxxado is intended for immediate administration as emergency therapy in settings where opioids may be present.
>
> Kloxxado is not a substitute for emergency medical care."

(b) (4)


In this supplement, the Applicant has submitted a comparative bioavailability study (Study NAL-NS0521/45) which was an open-label, randomized, single-dose, three-treatment, crossover, comparative bioavailability study of in healthy volunteers. The objective of this study was to evaluate comparative bioavailability of the proposed naloxone nasal spray 4 mg in comparison to Narcan nasal spray 4 mg and Kloxxado nasal spray 8 mg. This study was previously submitted and reviewed (b) (4)

### 3.3. Foreign Regulatory Actions and Marketing History

The currently proposed product is not approved anywhere in the world. Health Canada approved the 8 mg version of this product described in the parent marketing application (NDA 212045) on February 12, 2025.[88]

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations (OSI)

The Division of Pharmaceutical Manufacturing Assessment I (DPMAI), within the Office of Pharmaceutical Manufacturing Assessment (OPMA), has determined that further inspection is not warranted for this supplement.

### 4.2. Product Quality

In this supplement, the Applicant is using the same delivery device as the parent approved NDA (Kloxxado, 212045). The Office of Pharmaceutical Quality (OPQ), has determined that further inspection is not warranted for this supplement.

### 4.3. Clinical Microbiology

Not applicable.

## 4.4. Nonclinical Pharmacology/Toxicology

(b) (4)

In the current supplement (NDA 212045/S-005), a JAS (BIO-CTX-664) was submitted. Findings from that study supported the safety of the ethanol excipient in the neonatal population. Dr. Carlic Huynh, the primary reviewer, described the study as follows in his review submitted March 19, 2025:

> Briefly, juvenile rats were dosed with either saline vehicle control, Ethanol (b) (4) with Propylene Glycol (b) (4), or Ethanol (40%) with Propylene Glycol (b) (4) intranasally as a single dose. There were no deaths as well as no treatment-related changes in clinical signs, body weight and body weight gain, ophthalmoscopy, gross pathology, organ weights (brain and lung only), and histopathology (including the nasal cavity) at the end of the treatment and recovery periods. The results of the JAS support a lack of concern for the ethanol excipient in the neonatal population.

Thus, the Applicant has adequately addressed previous Nonclinical safety concerns. From the nonclinical pharmacology toxicology perspective, the proposed product has been recommended for approval.

## 4.5. Clinical Pharmacology

Study NAL-NS0521/45 (b) (4). Briefly, the study was an open-label, randomized, single-dose, three-treatment, three-period, crossover study in 69 adult male and female healthy volunteers under fasting conditions to determine the bioavailability of naloxone 4 mg or 8 mg nasal spray after an intranasal administration.

The treatment arms were:

- Treatment A: naloxone nasal spray, 4 mg (test drug)
- Treatment B: Narcan nasal spray, 4 mg (reference 1)
- Treatment C: Kloxxado nasal spray, 8 mg (reference 2)

The pharmacokinetic parameters of each treatment are presented in Table 3 and Figure 8. The proposed naloxone 4 mg nasal spray was demonstrated to result in systemic naloxone exposures that are between the two previously approved products (i.e., Narcan nasal spray 4 mg and Kloxxado 8 mg). In addition, these results suggest that the proposed product would have greater partial AUCs during early phase of absorption (e.g., $AUC_{0\text{-}2min}$, $AUC_{0\text{-}4min}$), greater $C_{max}$,

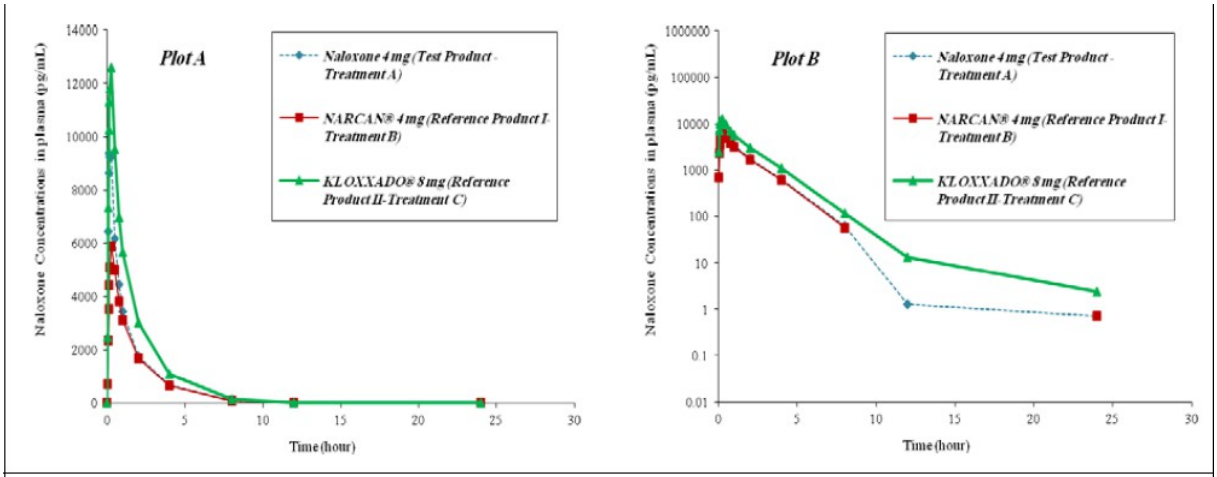
and greater $AUC_{0-t}$ and $AUC_{0-inf}$ values compared to naloxone 0.4 mg via IM injection [an ANDA 070256 product to the listed drug product (i.e., Narcan injection NDA 016636)], based on data from other comparative bioavailability studies previously submitted to the NDA. Naloxone 0.4 mg IM is considered to provide the lower limit of acceptable naloxone dose.

These results demonstrate that the proposed naloxone nasal spray product achieves comparable or greater systemic naloxone exposures as compared to Narcan, including, importantly, in the critical period immediately after drug administration. Therefore, the pharmacokinetic study data provide an adequate scientific bridge to rely on the Agency's previous finding of efficacy for Narcan.

Table 3. Mean Pharmacokinetic Characteristics of Naloxone After Administration of Naloxone 4 mg (Test Drug), Narcan Nasal Spray, 4 mg (Reference Product I), and Kloxxado Nasal Spray, 8 mg (Reference Product II)

| Pharmacokinetic Parameter | Treatment (Mean ± SD) | | |
|---|---|---|---|
| | Test Product (Treatment A) (N=71) | Reference Product I (Treatment B) (N=70) | Reference Product II (Treatment C) (N=70) |
| $C_{max}$ (pg/ml) | 11115.393±4639.53 | 6559.328±2352.57 | 14413.506±6799.07 |
| $C_{max-D}$ (pg/ml) | 2778.848±1159.88 | 1639.832±588.14 | 1801.688±849.88 |
| $AUC_{0\rightarrow t}$ (pg.h/ml) | 12307.8±3890.88 | 10144.4±3595.01 | 19569.5±6925.39 |
| $AUC_{0\rightarrow t\text{-}D}$ (pg.h/ml) | 3076.9±972.72 | 2536.1±898.75 | 2446.2±865.67 |
| $AUC_{0\rightarrow \infty}$ (pg.h/ml) | 12575.1±3851.14 | 10407.6±3520.29 | 19815.6±6881.43 |
| $AUC_{0\rightarrow \infty\text{-}D}$ (pg.h/ml) | 3143.8±962.79 | 2601.9±880.07 | 2476.9±860.18 |
| $AUC_{0\rightarrow 2min}$ (pg.h/ml) | 38.74±38.95 | 11.34±13.51 | 40.93±52.22 |
| $AUC_{0\rightarrow 4min}$ (pg.h/ml) | 188.06±149.02 | 62.95±56.31 | 207.97±200.34 |
| $AUC_{0\rightarrow 6min}$ (pg.h/ml) | 436.52±290.67 | 159.77±124.25 | 498.40±410.68 |
| $AUC_{0\rightarrow 8min}$ (pg.h/ml) | 733.50±443.88 | 290.80±202.42 | 854.30±631.74 |
| $AUC_{0\rightarrow 10min}$ (pg.h/ml) | 1049.9±598.10 | 452.33±284.42 | 1247.2±834.83 |
| $AUC_{0\rightarrow 15min}$ (pg.h/ml) | 1816.3±901.85 | 907.26±461.21 | 2259.2±1282.21 |
| $AUC_{0\rightarrow 30min}$ (pg.h/ml) | 3738.8±1477.04 | 2266.2±827.87 | 5023.2±2217.62 |
| $AUC_{0\rightarrow 45min}$ (pg.h/ml) | 5060.5±1747.81 | 3368.1±1066.31 | 7087.6±2718.34 |
| $AUC_{0\rightarrow 1hr}$ (pg.h/ml) | 6043.2±1920.89 | 4234.0±1248.82 | 8666.3±3071.20 |
| $t_{max}$ (h) * | 0.17 (0.07- 0.50) | 0.25 (0.13- 1.00) | 0.25 (0.07- 1.00) |
| $K_{el}$ (1/h) | 0.5657±0.10 | 0.5557±0.09 | 0.5369±0.11 |
| $t_{1/2el}$ (h) | 1.27±0.33 | 1.30±0.34 | 1.56±1.98 |
| $AUC_{0\rightarrow t}/AUC_{0\rightarrow \infty}$% | 97.58±2.47 | 96.85±3.19 | 98.48±1.86 |

Abbreviations: AUC, area under the curve; $C_{max}$, maximum observed plasma concentration; $K_{el}$, elimination rate constant; SD, standard deviation; $T_{max}$, time to maximum plasma concentration




Linear presentation (Plot A) and semi-logarithmic presentation (Plot B) for naloxone means after a single dose administration of one intranasal spray from treatments *Naloxone 4 mg*, 4 mg naloxone hydrochloride per one spray (Test Product), *NARCAN® 4 mg*, 4 mg naloxone hydrochloride per one spray (Reference Product I) and *KLOXXADO® 8 mg*, 8 mg naloxone hydrochloride per one spray (Reference Product II)

Figure 8. Presentation (Plot A) and Semi-logarithmic Presentation (Plot B) for Naloxone Means After a Single Dose Administration of One Intranasal Spray from Treatments Naloxone 4 mg, 4 mg Naloxone nasal spray, Narcan 4 mg and Kloxxado® 8 mg.

### 4.6. Devices and Companion Diagnostic Issues

The Applicant has used the same device as the approved Kloxxado (parent NDA 212045), except for the modification to the actuator spray pin. Based on Dr. Dr. López-Pérez's assessment, it was concluded that the proposed changes for the device will not impact the quality of the drug product nor the device performance.

### 4.7. Consumer Study Reviews

Hikma is proposing (b) (4)

The Agency acknowledged that the user interface, intended users, use environments, and use tasks of the proposed 4 mg naloxone nasal spray are the same as that of Kloxxado. Given that the only differences between the two products are the strength (4 mg versus 8 mg) and name (naloxone versus Kloxxado) and that the Agency previously reviewed the human factors data for Hikma's Kloxxado, it was determined that no additional human factors data are required to be submitted for the proposed 4 mg strength.

Refer to Dr. Damon Birkemeier's (DMEPA) review for complete details.

## 5. Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

No clinical studies of efficacy were submitted in support of this supplement.

### 5.2. Review Strategy

No clinical efficacy trials were conducted in support of this supplement, which relies on PK data and previous Agency findings of the efficacy of naloxone. The safety of the submitted product was assessed based on the safety evaluations completed as a part of the bridging PK study.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

As discussed in Section 4.5, the comparative bioavailability of a single 4 mg dose (one spray) of the proposed naloxone nasal spray versus a single dose of Kloxxado naloxone 8 mg nasal spray (NDA 212045) and a single dose of a previously approved Narcan naloxone 4 mg nasal spray established an adequate scientific bridge to the Agency's previous findings of efficacy for Narcan. No new efficacy studies were required to support this application, and no new clinical trial data were submitted.

## 7. Integrated Review of Effectiveness

See Sections 4.5 and 6.

## 8. Review of Safety

### 8.1. Safety Review Approach

Safety from Study NAL-NS0521/45 (b) (4) The following comments were abstracted (b) (4)

Overall, a total of 72 subjects were exposed to the naloxone nasal spray 4 mg (test drug), 70 subjects to Narcan nasal spray (reference 1), and 70 subjects to Kloxxado nasal spray 8 mg (reference drug 2) in the PK study. Sixty-nine subjects completed the study. The clinical laboratory testing from both studies were acceptable and provided some information to support the safety of using 4 mg naloxone nasal spray. The nasal irritation assessment tool and monitoring are adequate to evaluate the potential for local toxicity. The safety monitoring plan appears adequate for this population. No clinically significant findings were noted for any chemistry, hematology, or urinalysis results in any groups. There were no deaths, no serious

adverse events, and three cases of study discontinuation (two for personal reasons and one for a positive COVID-19 test). Overall, there are no newly identified safety signals.

## 8.2. Safety in the Postmarket Setting

### 8.2.1. Safety Concerns Identified Through Postmarket Experience

In general, naloxone has been widely marketed in the United States for over than 40 years with a well-known safety profile. The safety of naloxone has been under regular review through postmarketing studies. Based on the available data from spontaneous reporting and literature review (and as summarized in Section 2.2), key safety concerns with naloxone include the risks of precipitated withdrawal and noncardiogenic pulmonary edema. However, the frequency and severity of these events are typically low and considered to be acceptable given the clear life-saving benefits of naloxone administration for opioid overdose.

### 8.2.2. Expectations on Safety in the Postmarket Setting

Safety of the currently proposed product is expected to be consistent with that of other approved naloxone nasal spray products.

### 8.2.3. Additional Safety Issues From Other Disciplines

No safety concerns were raised by the other review disciplines.

## 8.3. Integrated Assessment of Safety

Review of the safety data from Study NAL-NS0521/45 revealed no new safety signals with use of 4 mg nasal naloxone. There were no clinically significant adverse events noted. Review of local toxicity on nasal cavity and olfactory function did not raise any safety concerns.

There is a risk of precipitated withdrawal after naloxone administration in persons with opioid dependence, which may unfortunately discourage more widespread use of naloxone among the very population that is at the greatest risk of opioid overdose and would be most likely to benefit from naloxone availability. Although the risk of precipitated withdrawal increases with higher naloxone exposures, no specific doses or formulations of naloxone have been implicated as being particularly more likely to precipitate withdrawal. Other adverse events, including cardiovascular events, pulmonary edema, and seizures, have been reported in the presented literature. However, these events are rare, and separating these effects of naloxone from the effects of concomitant medications and pre-existing disorders have been problematic. Thus, overall, naloxone is considered to have a wide safety margin.

# 9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held to discuss this product because there were no issues that required presentation or discussion at an advisory committee meeting.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

The Division of Medical Error Prevention and Analysis (DMEPA 1) and Office of Medication Error Prevention and Risk Management (OMEPRM), and the Office of Surveillance and Epidemiology (OSE) were consulted regarding the proposed labeling. As discussed later in this review, the Full Prescribing Information for the Kloxxado 4 mg and 8 mg products were combined to emphasize to prescribers, to the greatest extent possible, the minor differences between the products. We also added language to the Highlights of Prescribing Information emphasizing: 1) nominal dose and exposure are different and that all approved naloxone hydrochloride-containing products are considered safe and effective, and 2) the chance of opioid withdrawal increases with increasing dose/exposure in opioid-dependent individuals.

## 10.2. Nonprescription Drug Labeling

Not applicable.

# 11. Risk Evaluation and Mitigation Strategies (REMS)

The review team has determined that a REMS is not necessary to assure a positive benefit-risk profile for the proposed drug product.

# 12. Postmarketing Requirements and Commitments

As described in 1.5 Patient Experience Data, patients and advocates have expressed concerns regarding high-exposure products like the one reviewed in this supplement (and its parent product) because of a reasonable concern for increased harms—in particular, increased risk of precipitated withdrawal—without an attendant benefit or increase in efficacy. While the data submitted by the Applicant meet the evidentiary threshold needed for an approval via the 505(b)(2) pathway, they do not make or support any claims that differentiate the proposed product from other existing approved products, including the parent NDA. It is unclear whether prescribers would have adequate information to distinguish from among the proposed naloxone 4 mg nasal spray, the parent naloxone 8 mg nasal spray, and the OTC naloxone 4 mg nasal spray.

As described in 2.2 Analysis of Current Treatment Options, recent epidemiological trends include the unacceptably high but declining rates of fatal and non-fatal opioid overdose, greater availability of OTC and prescription naloxone products, and increased involvement of non-opioid substances in opioid-related overdoses. This changing landscape of opioid overdose is the backdrop for more prominent concerns from patients and advocates about higher-dose naloxone products and the risk of precipitated withdrawal.

Accordingly, the primary clinical reviewer, Dr. Zachary Dezman, recommended the following post-marketing requirements:

> The Applicant should conduct a study examining the incidence of precipitated withdrawal and noncardiogenic pulmonary edema among opioid-dependent patients of their product.

The Applicant should provide comparative safety data to assist prescribers in differentiating between their 4 mg and 8 mg products.

## 13. CDTL/Division Director Assessment

The Applicant has provided substantial evidence of safety and effectiveness with study NAL-NS0521/45, a PK study that demonstrates plasma concentrations with the proposed drug product are higher than with Narcan 4 mg and lower than Kloxxado 8 mg, which establishes an adequate scientific bridge for reliance on efficacy findings of the reference drug Narcan 4 mg nasal spray, and on the systemic safety findings of Kloxxado 8mg. (b) (4) [redacted]. Thus, there are no outstanding issues that would preclude approval of this supplement from the Product Quality, Nonclinical Pharmacology/Toxicology, Clinical Pharmacology, or Clinical perspectives.

Given the Applicant's existing Kloxxado 8 mg nasal spray and OTC Narcan 4 mg nasal spray, the potential approval of this Applicant's naloxone 4 mg nasal spray does raise concerns regarding the ability of prescribers, patients, and caregivers to select the most appropriate naloxone product for a given patient. We acknowledge the concerns raised by Dr. Dezman, patients, and advocates regarding the risks of precipitated withdrawal with higher-exposure naloxone products, such as the currently proposed product, especially given evolving national trends in opioid overdoses. Despite the rapid expansion in available ORAs in recent years, key knowledge gaps remain regarding higher-exposure naloxone products 1) as compared to lower dose and/or OTC naloxone products, and 2) in opioid-dependent persons, who are among the most likely to require emergency naloxone administration and are also at greatest risk of precipitated withdrawal.

There are no comparative efficacy or safety data to distinguish among the various naloxone nasal spray products. Thus, while there is insufficient evidence to guide product selection,

there is also insufficient evidence to support that any of the approved products is less effective or less safe than any other. We concur with the proposed labeling recommendations to include information that reflects the available data:

- All approved naloxone products are considered safe and effective for reversal of opioid overdose.
- Nominal dosage does not directly translate to naloxone exposure, and comparison of naloxone products on a mg-per-mg basis may be misleading.
- Higher naloxone exposures are associated with increased risk of precipitated withdrawal following opioid overdose reversal.

A PMR mandating the collection of comparative safety and efficacy data between the Applicant's two nasal spray products has been considered. However, it must be emphasized that although the currently proposed product results in naloxone exposures exceeding that of other naloxone 4 mg nasal spray products, the exposures of this product are below those of other approved naloxone nasal sprays, including Kloxxado 8 mg nasal spray. Furthermore, with the approval of Rezenopy (NDA 215487), a 10 mg nasal spray, in April 2024, no safety PMRs were required. Thus, a PMR for this product cannot be justified considering that other recently approved products may pose greater risks. Moreover, a comparative safety study of this Applicant's two naloxone nasal spray products, as proposed by Dr. Dezman, would not provide sufficient data to address the concern that higher-dose naloxone products in general may present greater risks than lower-dose products. Similarly, a PMR solely for this product mandating a study in opioid-dependent persons cannot be justified.

This regulatory action for this application is approval.

# 14. Appendices

## 14.1. References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## 14.2. Financial Disclosure

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator", certifying that they had no financial interests or arrangements with clinical investigators were made which could affect the outcome of effect the outcome of the studies as defined in 21 CFR 54.2(a) and no listed investigators were the recipients of significant payments of other sort as defined in 21 CFR 54.2(f). There was one Principal investigator involved in the PK study.

Covered Clinical Study (Name and/or Number): NAL-NS0521/45

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 1 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 0<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in Sponsor: 0<br>Sponsor of covered study: 0 | | |
| 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) 0 | | |
| Is an attachment provided with the | Yes ☐ | No ☐ (Request explanation |

| | | |
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| reason: | | from Applicant) |

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/s/

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