Office of Clinical Pharmacology Review

NDA or BLA Number	212045 S-005
Link to EDR	\\CDSESUB1\evsprod\NDA212045\0191
Submission Date	10/25/2024; PDUFA date: 8/25/2025
Submission Type	Standard; Efficacy Supplement 505(b)(2)
Brand Name	Kloxxado (naloxone hydrochloride) nasal spray
Generic Name	Naloxone hydrochloride (HCl) nasal spray
Dosage Form and Strength	Solution for pre-filled intranasal spray device Approved Strength: one spray (0.1 mL) delivers 8 mg naloxone hydrochloride Proposed Additional Strength: one spray (0.1 mL) delivers 4 mg naloxone hydrochloride
Route of Administration	Intranasal
Indication	• KLOXXADO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults 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.
Dosage and Administration	• KLOXXADO is for intranasal use only. • Seek emergency medical care immediately after use. • Administer a single spray of KLOXXADO to adult or pediatric patients intranasally into one nostril. • Administer additional doses of KLOXXADO, using a new nasal spray with each dose, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses of KLOXXADO may be given every 2 to 3 minutes until emergency medical assistance arrives. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.
Applicant	Hikma Pharmaceuticals USA Inc
Associated IND	IND 134954
OCP Reviewer	Wei Qiu, Ph.D.
OCP Team leader	Deep Kwatra, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the information submitted in the current application, NDA 212045 efficacy supplement S-005, for Naloxone HCl nasal spray 4 mg, submitted on 10/25/2024. In this efficacy supplement S-005, the Applicant submitted a comparative bioavailability study NAL-NS0521/45. Study NAL-NS0521/45 (b) (4) was reviewed and found reliable to support the Applicant's proposed reliance on efficacy findings of Narcan (naloxone HCl) nasal spray 4 mg (NDA 208411) and systemic safety findings of the Applicant's approved Kloxxado (naloxone HCl) nasal spray 8 mg (NDA 212045) (see Clinical Pharmacology Review dated 10/27/2022 and Addendum about OSIS inspection of Study NAL-NS0521/45 on 11/7/2022 in DARRTS). From a clinical pharmacology perspective, the information submitted in the NDA supplement submission is acceptable.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

- **Regulatory History**

The Applicant submitted a 505(b)(2) NDA 202145 efficacy supplement S-005 on 10/25/2024, to add a new lower strength naloxone nasal spray 4 mg (4 mg in 0.1 mL in a pre-filled intranasal device designed to deliver a single spray of 4 mg naloxone HCl) to the approved NDA 212045 (Kloxxado nasal spray 8 mg). Per Form 356h, Narcan (naloxone HCl) injection (NDA 016636) and Narcan nasal spray 4 mg (NDA 208411) were identified as the listed drugs to support this 505(b)(2) NDA 212045 S-005. The Applicant also made reference to their own NDA 212045 for Kloxxado nasal spray 8 mg.

The Kloxxado nasal spray 8 mg was approved under NDA 212045 on 4/29/2021. It relied on the FDA's previous finding of safety and efficacy for Narcan injection (NDA 016636). The Applicant

conducted two comparative bioavailability studies (Studies INS012-17-108 and Study INS012-18-119) to characterize the PK of Kloxxado nasal spray 8 mg and to establish a scientific bridge between Kloxxado nasal spray 8 mg and Narcan injection (NDA 016636) at 0.4 mg IM dose. Because the original NDA 016636 for Narcan injection was withdrawn not for reasons of safety or efficacy, a generic product (ANDA 072076) to the original NDA 016636 was used as the comparator in the comparative bioavailability studies to establish the scientific bridge.

The proposed naloxone nasal spray 4 mg product (b) (4) the Applicant submitted a comparative bioavailability Study NAL-NS0521/45 which showed that naloxone nasal spray 4 mg demonstrated higher plasma concentrations at the early absorption phase, greater C_{max}, greater AUC_{0-t} and AUC_{0-inf} than Narcan nasal spray 4 mg (NDA 208411) and lower C_{max}, AUC_{0-t}, and AUC_{0-inf} than Kloxxado nasal spray 8 mg (NDA 212045). Therefore, naloxone nasal spray 4 mg was demonstrated that the naloxone systemic exposures were between that of Narcan nasal spray 4 mg and Kloxxado nasal spray 8 mg, supporting the Applicant's proposed reliance on efficacy findings of Narcan nasal spray 4 mg and systemic safety findings of Kloxxado nasal spray 8 mg. Based on the OSIS review in DARRTS dated 11/1/2022, the inspections in the clinical site (International Pharmaceutical Research Center (IPRC)) (b) (4) for study NAL-NS0521/45 were not needed. The rationale included (1) the Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in July 2022, which fell within the surveillance interval. After review of the inspectional findings, OSIS concluded that data from the reviewed studies were reliable; and (2) OSIS conducted a Remote Regulatory Assessment (RRA) for the (b) (4), which fell within the surveillance interval. OSIS concluded that data from the reviewed studies were reliable. (b) (4)

(b) (4)

In this efficacy supplement S-005, the Applicant submitted a comparative bioavailability study NAL-NS0521/45. Study NAL-NS0521/45 (b) (4) and found reliable to support the Applicant's proposed reliance on efficacy findings of Narcan nasal spray 4 mg and systemic safety findings of Kloxxado nasal spray 8 mg (see

Clinical Pharmacology Review dated 10/27/2022 and Addendum regarding OSIS inspection on 11/7/2022 in DARRTS). This review focuses on review of proposed labeling.

- **Summary of Pharmacokinetic Results**

The following is from Clinical Pharmacology Review [redacted] (b) (4)

(1) Comparative Bioavailability of Proposed Naloxone HCl Nasal Spray 4 mg and Approved Kloxxado Nasal Spray 8 mg (Results from Study NAL-NS0521/45)

The proposed Naloxone HCl nasal spray 4 mg showed a similar median Tmax (0.17 hour) compared to Kloxxado nasal spray 8 mg (0.25 hour). A single 4 mg dose of Naloxone HCl nasal spray 4 mg exhibited slightly lower naloxone concentrations during the early absorption phase (e.g., 2, 4, 6, 8, 10 min post-dose), 23% lower Cmax, and 35% to 36% lower AUC0-t and AUC0-inf values than a single 8 mg dose of Kloxxado nasal spray 8 mg. Naloxone HCl nasal spray 4 mg showed 29% greater bioavailability in terms of dose normalized AUC0-inf (AUC0-inf/Dose) than Kloxxado nasal spray 8 mg because the geometric mean ratio (90%CI) for AUC0-inf/Dose for Naloxone HCl nasal spray 4 mg/Kloxxado nasal spray 8 mg was 129.27% (120.73% - 138.40%).

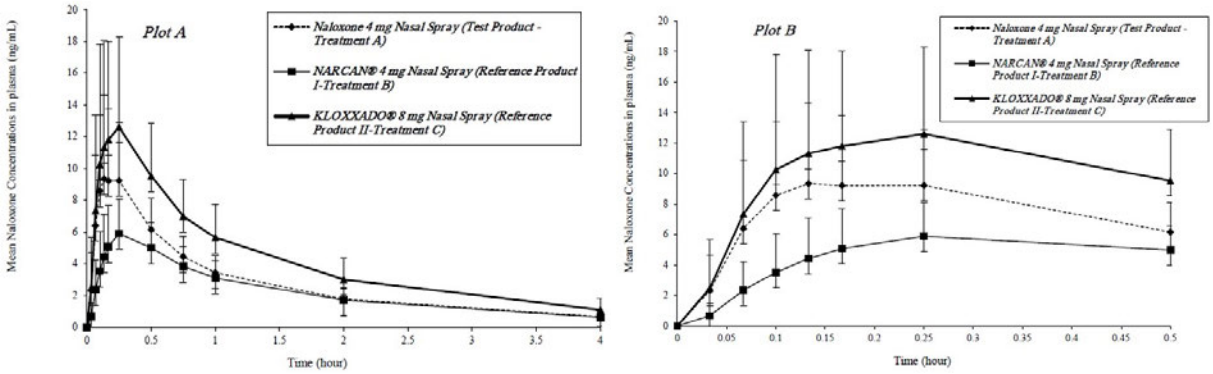
Study NAL-NS0521/45 was a randomized, single-dose, three-period, three-sequence crossover study in healthy adults under fasting conditions. The primary objectives were to investigate the bioequivalence of the proposed Naloxone HCl nasal spray 4 mg relative to Narcan nasal spray 4 mg after an intranasal administration and to compare the PK parameters after an intranasal administration of Naloxone HCl nasal spray 4 mg and Kloxxado nasal spray 8 mg. Seventy-two (72) fasted male subjects were enrolled. Study participants received a single dose of Naloxone HCl nasal spray 4 mg (Test Product, Treatment A), Narcan nasal spray 4 mg (Reference Product I, Treatment B) and Kloxxado nasal spray 8 mg (Reference Product II, Treatment C) in a randomized manner with 7 days of washout period between treatment periods. Test and reference products were given via intranasal administration of one spray (single actuation) administered in one nostril. Blood samples for determination of free naloxone concentrations in plasma were collected prior to dosing and at 2, 4, 6, 8, 10, 15, 30, and 45 minutes, and 1, 2, 4, 8, 12, and 24 hours post-dose for each treatment.

The mean (± SD) naloxone plasma concentration-time profiles following a single dose of one intranasal spray Naloxone HCl nasal spray 4 mg (Test Product, Treatment A) versus Narcan nasal spray 4 mg (Reference Product I, Treatment B) and Kloxxado nasal spray 8 mg (Reference Product II, Treatment C) are shown in **Figure 1**. Naloxone PK parameters are summarized in **Table 1**. The comparison of naloxone AUC0-t, AUC0-inf, and dose normalized AUC0-t (AUC0-t/Dose) and AUC0-inf/Dose for Naloxone HCl nasal spray 4 mg and Kloxxado nasal spray 8 mg are shown in **Table 2**.

The median Tmax (min, max) values were similar: median (min, max) Tmax values were 0.17 (0.07 to 0.50) h, 0.25 (0.13 to 1.00) h, and 0.25 (0.07 to 1.00) h for the proposed Naloxone HCl nasal spray 4 mg, Narcan nasal spray 4 mg, and Kloxxado nasal spray 8 mg, respectively. Mean half-life values of naloxone were approximately 1.27 to 1.56 hours for all treatments (**Table 1**).

Naloxone HCl nasal spray 4 mg exhibited lower naloxone concentrations during the early absorption phase (e.g., 2, 4, 6, 8, 10 min post-dose) and throughout the entire sampling period than Kloxxado nasal spray 8 mg (**Figure 1**). Naloxone HCl nasal spray 4 mg showed 23% lower Cmax and slightly lower partial AUCs during the early absorption phase (**Table 1**). Statistical analysis of AUC0-t and AUC0-inf showed that Naloxone HCl nasal spray 4 mg exhibited 36% lower AUC0-t and 35% lower AUC0-inf values than Kloxxado nasal spray 8 mg (**Table 2**). Naloxone HCl nasal spray 4 mg showed approximately 30% greater bioavailability in terms of dose normalized AUC0-t/Dose and AUC0-inf/Dose than Kloxxado nasal spray 8 mg because the geometric mean ratios (90%CI) for dose-normalized naloxone AUC0-t (AUC0-t/Dose) and AUC0-inf (AUC0-inf/Dose) were 128.06% (119.28% - 137.49%) and 129.27% (120.73% - 138.40%), respectively (**Table 2**).

Figure 1 Mean (± SD) Plasma Concentration Time Profiles of Naloxone Following a Single Dose of One Intranasal Spray Naloxone HCl Nasal Spray 4 mg (Test Product, Treatment A) versus Narcan Nasal Spray 4 mg (Reference Product I, Treatment B) and Kloxxado Nasal Spray 8 mg (Reference Product II, Treatment C) (Plot A: 0-4 h and Plot B: 0-0.5 h) (Study NAL-NS0521/45)



Source: Proposed label based on Study report NAL-NS0521/45

Table 1 Mean ± SD (%CV) Naloxone Pharmacokinetic Parameters for Naloxone HCl Nasal Spray 4 mg (Test Product, Treatment A), Narcan Nasal Spray 4 mg (Reference Product I, Treatment B), and Kloxxado Nasal Spray 8 mg (Reference Product II, Treatment C) (Study NAL-NS0521/45)

PK Parameter	**Naloxone HCl nasal spray 4 mg (Test, Treatment A) (N = 71)**	**Narcan nasal spray 4 mg (Reference Product I, Treatment B) (N = 70)**	**Kloxxado nasal spray 8 mg (Reference Product II, Treatment C) (N = 70)**
Tmax (h)*	0.17 (0.07 – 0.50)	0.25 (0.13 – 1.00)	0.25 (0.07 – 1.00)
Cmax (pg/mL)	11115.393 ± 4639.53 (41.74%)	6559.328 ± 2352.57 (35.87%)	14413.506 ± 6799.07 (47.17%)
Cmax/Dose (pg/mL/mg)	2778.848 ± 1159.88	1639.832 ± 588.14	1801.688 ± 849.88
AUC0-t (pg.h/mL	12307.8 ± 3890.88 (31.61%)	10144.4 ± 3595.01 (35.44%)	19569.5 ± 6925.39 (35.39%)
AUC0-t/Dose (pg.h/mL/mg)	3076.9 ± 972.72	2536.1 ± 898.75	2446.2 ± 865.67
AUC0-inf (pg.h/mL)	12575.1 ± 3851.14 (30.63%)	10407.6 ± 3520.29 (33.82%)	19815.6 ± 6881.43 (34.73%)
AUC0-inf/Dose (pg.h/mL/mg)	3143.8 ± 962.79	2601.9 ± 880.07	2476.9 ± 860.18
AUC0-2min (pg.h/mL)	38.74 ± 38.95 (100.56%)	11.34 ± 13.51 (119.13%)	40.93 ± 52.22 (127.58%)

AUC0-4min (pg.h/mL)	188.06 ± 149.02 (79.24%)	62.95 ± 56.31 (89.45%)	207.97 ± 200.34 (96.33%)
AUC0-6min (pg.h/mL)	436.52 ± 290.67 (66.59%)	159.77 ± 124.25 (77.77%)	498.40 ± 410.68 (82.40%)
AUC0-8min (pg.h/mL)	733.50 ± 443.88 (60.52%)	290.80 ± 202.42 (69.61%)	854.30 ± 631.74 (73.95%)
AUC0-10min (pg.h/mL)	1049.9 ± 598.10 (56.97%)	452.33 ± 284.42 (62.88%)	1247.2 ± 834.83 (66.94%)
Kel (1/h)	0.5657 ± 0.10 (16.90%)	0.5557 ± 0.09 (16.66%)	0.5369 ± 0.11 (21.22%)
T1/2 (h)	1.27 ± 0.33 (26.32%)	1.30 ± 0.34 (26.22%)	1.56 ± 1.98 (126.82%)**

*Reported as median (min, max); ** subject #20 has a half-life of 17.62 h, excluding this subject the mean half-life is 1.33 h
Source: Study report NAL-NS0521/45 Table 5, section 14.2 Tables 9, 10 and 11.

Table 2 Statistical Analysis of Naloxone AUC0-t, AUC0-t/Dose, AUC0-inf, and AUC0-inf/Dose after an Intranasal Administration of Naloxone HCl Nasal Spray 4 mg (Test) and Kloxxado Nasal Spray 8 mg (Reference) to Healthy Volunteers under Fasting Conditions (From Study NAL-NS0521/45)

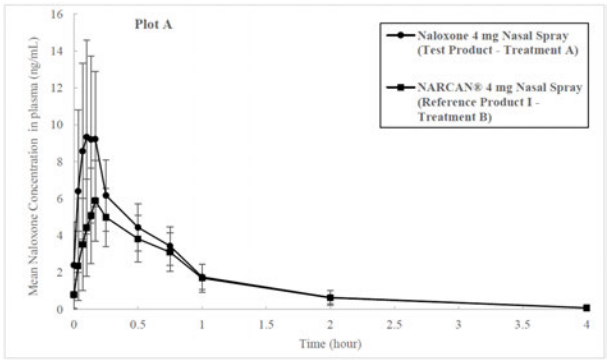
Parameter	**Geometric Least Squares Means (%)**			
	Naloxone HCl nasal spray 4 mg (Test)	**Kloxxado nasal spray 8 mg (Reference)**	**Ratio**	**90% CI**
AUC0-t (pg.h/mL)	11713.9	18293.1	64.03	59.64 – 68.74
AUC0-t/Dose (pg.h/mL/mg)	2928.5	2286.6	128.06	119.28 – 137.49
AUC0-inf (pg.h/mL)	12008.5	18578.9	64.63	60.36 – 69.20
AUC0-inf/Dose (pg.h/mL/mg)	3002.1	2322.4	129.27	120.73 – 138.40

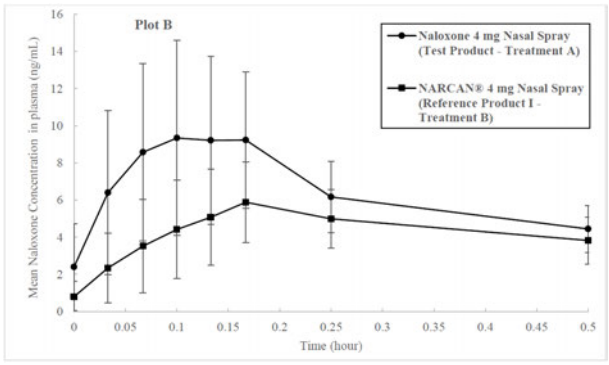
Source: Study report NAL-NS0521/45 Table 4

(2) Comparative Bioavailability of Proposed Naloxone HCl Nasal Spray 4 mg and Narcan Nasal Spray 4 mg (NDA 208411) (from Study NAL-NS0521/45)

The proposed Naloxone HCl nasal spray 4 mg showed a similar median Tmax (0.17 hour) compared to Narcan nasal spray 4 mg (0.25 hour) (**Table 1**). The mean AUC0-2min, AUC0-4min, AUC0-6min, AUC0-8min, and AUC0-10min for a single 4 mg dose of Naloxone HCl nasal spray 4 mg were 342%, 299%, and 273%, 252%, and 232% of that for a single 4 mg dose of Narcan nasal spray 4 mg (**Figure 2** and **Table 1**). Statistical analysis showed that Naloxone HCl nasal spray 4 mg exhibited 65% greater Cmax, 23% greater AUC0-t, and 22% greater AUC0-inf values than Narcan nasal spray 4 mg. The geometric ratios (90% CI) for Cmax, AUC0-t, and AUC0-inf for Naloxone HCl nasal spray 4 mg/Narcan nasal spray 4 mg were 165.30% (151.74% - 180.07%), 123.14% (114.70% - 132.20%), and 122.21% (114.14% - 130.85%), respectively. The bioequivalence was not demonstrated between the proposed Naloxone HCl nasal spray 4 mg and Narcan nasal spray 4 mg because the geometric ratios and 90% confidence intervals for Cmax, AUC0-t and AUC0-inf did not fall in the 80 – 125% bioequivalence criteria (**Table 3**).

Figure 2 Mean ± SD Plasma Concentration Time Profiles of Naloxone Following a Single Dose of One Intranasal Spray Naloxone HCl Nasal Spray 4 mg (Test Product, Treatment A) versus Narcan Nasal Spray 4 mg (Reference Product I, Treatment B) (Plot A: 0-4 h and Plot B: 0-0.5 h) (Study NAL-NS0521/45)





Source: July 21, 2022, submission cover letter

Table 3 Statistical Analysis of PK Parameters of Naloxone after an Intranasal Administration of Naloxone HCl Nasal Spray 4 mg (Test) and Narcan Nasal Spray 4 mg (Reference) to Healthy Volunteers under Fasting Conditions (From Study NAL-NS0521/45)

Parameter	**Geometric Least Squares Means (%)**			
	Naloxone HCl nasal spray 4 mg (Test)	**Narcan nasal spray 4 mg (Reference)**	**Ratio**	**90% CI**
Cmax (pg/mL)	10230.868	6189.121	165.30	151.74 – 180.07
AUC0-t (pg.h/mL)	11713.9	9512.3	123.14	114.70 – 132.20
AUC0-inf (pg.h/mL)	12008.5	9825.9	122.21	114.14 – 130.85

Source: Study report NAL-NS0521/45 Table 3

Reviewer Comments: No new clinical pharmacology information was submitted under this supplement and the currently discussed information has already been reviewed and deemed acceptable from a clinical pharmacology perspective. In this review cycle the main focus is on the labeling language with regards to use of the product in a prescription setting. The labeling negotiations were ongoing at the time of the finalization of the review. The suggested labeling changes are discussed in the next section of the review.

3. SUMMARY OF LABELING RECOMMENDATIONS

As of today (3/12/2025), labeling negotiation is still ongoing. Tentative labeling recommendations are shown below: recommended ~~deletions~~ are shown as red strikethrough and additions are shown as blue underlined text:

(b) (4)

[redacted]

6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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