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Drug Class Update: Opioid Reversal Agents

Date of Review: October 2023

Date of Last Review: March 2016
Dates of Literature Search: 01/01/2016 - 08/04/2023

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this update is to evaluate new evidence for the efficacy and safety of opioid reversal products and evaluate the place in therapy for recently approved medications.

Plain Language Summary:
- Two medicines, naloxone and nalmefene, are used to reverse the dangerous adverse effects of opioid overdose, including respiratory depression, sedation and low blood pressure. These medicines are sprayed into the nose or injected into the muscle or vein. People without medical training can give these medicines to someone who has overdosed.
- Evidence shows that injections of naloxone worked faster than the nasal spray. People receiving naloxone injections were also less likely to need a second dose of medicine to reverse the opioid overdose. Naloxone nasal spray may not fully reverse overdose symptoms if the person has taken a large amount of opioids or used a potent opioid such as fentanyl.
- Evidence shows that when naloxone is use in the community setting, not given by a medical professional, can decrease deaths due to opioid overdoses.
- The Veterans Administration (VA) recommends that veterans have access to naloxone nasal spray if they have a history of taking opioids on an ongoing basis or are at risk of overdosing on opioids. This guidance was published prior to the approval of the nalmefene nasal spray.
- The Oregon Health Plan (OHP) will pay for preferred naloxone injection or nasal spray for Fee-for-service (FFS) members. The Drug Use Research and Management Group recommends no changes to the current opioid reversal policy.

Research Questions:
1. What is the comparative effectiveness of opioid reversal agents when administered in the community by people without specific medical training (e.g., bystanders or first responders)?
2. What is the comparative effectiveness of opioid reversal agents based on route of administration when administered in the community by people without specific medical training?
3. What are the differences in harms of opioid reversal products for people who have an opioid overdose?
4. What is the evidence for efficacy in different subpopulations (e.g., type of opioid taken, route of opioid reversal agent)?

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Conclusions:

- There were 2 systematic reviews, 1 high quality guideline, 6 new formulations and one new safety warning published since the last review.
- A review published in June 2023 by the Drug Effectiveness Review Project (DERP) evaluated naloxone products (intramuscular [IM], intravenous [IV] and intranasal [IN]) for reversal of an opioid overdose. Most doses were given by a medical professional and only one study evaluated reversal with overdoses from fentanyl. There was moderate quality evidence that IM naloxone had a quicker time to response compared to IN formulations, and patients were less likely to require a second dose. There were no differences in hospitalizations. High dose naloxone was associated with a quicker response and less need for a second dose of naloxone (moderate quality evidence). One study comparing IM and IV naloxone found no difference in response time between formulations (very low quality evidence).
- A Canadian Agency for Drugs and Technology (CADTH) review on the use of naloxone in the community setting found low quality evidence that naloxone use by non-medical professionals reduced mortality due to fatal overdoses.
- Guidance from the Veterans Administration (VA) recommends the IN naloxone formulation be made available to all patients with opioid use disorder (OUD) or other risk factors for opioid overdose.
- Six new opioid reversal therapies, including 2 over-the-counter (OTC) products, were recently approved by the Food and Drug Administration (FDA).
- A warning for IN naloxone (NARCAN) was updated in the FDA labeling to include the risk of incomplete opioid reversal in the presence of potent or high dose opioid exposure.
- Limited data comparing different routes of opioid reversal therapies suggest similar adverse events (AEs) including headache, nausea and vomiting.
- There is limited evidence evaluating the use of opioid reversal agents given by non-medical professionals. Additional studies are needed to evaluate the most effective opioid reversal agents for high dose, synthetic opioid analogs, such as fentanyl.

Recommendations:

- No changes to the preferred drug list are recommended based on review of the current evidence.
- After evaluation of costs in executive session, over-the-counter reversal agents were added as covered products. Additionally, OPVEE (nalmefene) and naloxone cartridges were made preferred on the PDL.

Summary of Prior Reviews and Current Policy:

- The previous March 2016 review found no differences in effectiveness or harms between injectable and intranasal naloxone to reverse opioid overdose.
- Increased access to naloxone for opioid users at high risk for opioid overdose is recommended by local and national organizations due to low quality evidence that increased naloxone availability in the community reduces rates of opioid overdose deaths.

Background:

Drug overdoses have become a national epidemic in the US with unintentional opioid overdose deaths rising annually in Oregon since 2019.[1] In a 12-month period ending in October 2022, there were more than 101,750 reported fatal opioid overdoses in the US.[2] Deaths from opioids occur most often in those 18 to 65 years and in children 15-19 years of age.[3] In October 2017, the United States (US) federal government declared the opioid epidemic a public health emergency.[4] There has been a large increase the deaths of teens contributing to these statistics which is thought to be due in part to the availability of illegal synthetic opioids, such as fentanyl. Additional scenarios which may lead to opioid overdose include: initiating medication that may compete for the same metabolic pathway; addition of a medication that may also affect the central nervous system; concomitant alcohol use; and inadvertently taking a higher dose

than prescribed to help better manage pain. All 50 states have policies called naloxone access law which are designed to expand access of naloxone for layperson use.[3] Despite efforts to increase distribution and use of opioid reversal agents, barriers still exist which prevent access.

Opioids can be lethal due to their ability to cause respiratory and central nervous system depression. Opioid reversal agents are antagonists at the opioid receptor which cause reversal of the effects of opioids (e.g., sedation, hypotension, and respiratory depression) and prevent hypoxia-associated injury and death.[3] The World Health Organization (WHO) and the American Society of Addiction Medicine (ASAM) recommend that people with OUD and those likely to witness an opioid overdose should have naloxone accessible.[5] Naloxone and nalmefene are the two opioid reversal agents approved by the FDA. Naloxone and nalmefene are available in several formulations: IM, IN, IV and SQ. Naloxone remains effective for 20-90 minutes after administration. Nalmefene has a longer half-life than naloxone and may be advantageous when overdoses occur in people who have taken opioids that have a longer half-life.[4] Prior to 2023, all opioid reversal products required a prescription. In 2023, the FDA approved 2 over-the-counter IN naloxone products, NARCAN and REVIVE (**Table 1**). Absorption differs across different tissue types, and therefore, doses differ depending on the route of administration. Evidence for naloxone suggests that the IM formulation has a quicker onset of action, approximately 2 minutes faster, compared to the IN route.[6] This difference is considered clinically meaningful according the DERP.[6]

There is no evidence to evaluate what dose of naloxone is needed to counteract the effects of potent opioids, such as fentanyl, or high-dose opioids. The Centers for Disease Control and Prevention (CDC) has recommended that patients be counseled that multiple does of naloxone may be needed to treat a single overdose attack due to the potency and prolonged effects of potent fentanyl analogs.[7]

Table 1. FDA Approved Opioid Reversal Products

Drug	Route of Administration	Prescription Status	Community Use
Naloxone[8]	Injectable 0.02 mg, 0.4 mg or 1 mg per vial (IM, IV, SQ)	Prescription	No
Naloxone[8]	Nasal 2 mg and 4 mg	Prescription	Yes
Naloxone (Narcan®)[9]	Nasal 4 mg	OTC	Yes
Naloxone (ReVive™)[10]	Nasal 3 mg	OTC	Yes
Naloxone (Kloxxado®)[11]	Nasal 8 mg	Prescription	Yes
Naloxone (Zimhi®)[12]	Injectable 5 mg per syringe (IM or SQ)	Prescription	Yes
Naloxone (Rextovy™)[13]	Nasal 4 mg	Prescription	Yes
Nalmefene[14]	Injectable 2 mg (IM, IV, SQ)	Prescription	No
Nalmefene (Opvee®)[15]	Nasal 2.7 mg	Prescription	Yes
Abbreviations: IM = intramuscular; IV = intravenous; OTC = over the counter; SQ = subcutaneous			

Important outcomes for opioid reversal agents include response or reversal of overdose symptoms, time-to-response, number of people needing a second dose, hospital admission rates and adverse effects (AEs). It is recommended that those requiring an opioid reversal agent be evaluated by a medical professional but not all require hospitalization.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence

(NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

DERP – Effectiveness and Harms of Naloxone for Opioid Overdose

A recent publication by DERP evaluated the different FDA-approved naloxone products used for opioid overdose.[6] Twelve randomized and nonrandomized trials and cohort studies evaluating naloxone delivered by the IN and IM routes were included (**Table 1**). Five of the studies were randomized controlled trials (RCTs) (all compared IN naloxone to IM or IV naloxone) and 7 were nonrandomized cohort studies.[6] None of the RCTs were conducted in the United States (US). Intranasal naloxone was compared to IM naloxone in 4 studies, four studies compared IN naloxone with IV naloxone, one study compared IM naloxone with IV naloxone, and three studies compared low-dose naloxone with high-dose naloxone. Naloxone doses included in the studies ranged from 0.4 mg to 2 mg, which the maximum dose is lower than currently available high-dose naloxone products. Participants included in the studies were mostly adult males.[6] All studies looked at initial reversal of opioid overdose symptoms and without long-term follow-up. A majority of studies evaluated doses administered by a medical professional. The most common opioids involved in overdoses were opium and heroin, only one study included participants who had fentanyl exposure.[6] Response time was measured 8 to 10 minutes after administration.

Table 1. Naloxone Products Included in the DERP Report[6]

Drug	Route of Administration	FDA Approval Date
Naloxone	Injectable 0.02 mg, 0.4 mg or 1 mg per vial	1971
Naloxone (Narcan®)	Nasal 4 mg	11/18/2015
Naloxone	Nasal 2 mg and 4 mg	4/19/2019
Naloxone (Kloxxado®)	Nasal 8 mg	4/29/2021
Naloxone (Zimhi®)	Injectable 5 mg	10/15/2021

The results of the DERP review are presented in **Table 2**. All formulations effectively reversed opioid overdose; however some required additional doses. Intramuscular naloxone was found to have a quicker onset than the IN formulation. Withdrawal symptoms were more common with the IM dosage form.

Table 2. Key Findings from Naloxone Trials Included in the DERP Report[6]

Comparison	Results	Quality of Evidence
IN naloxone vs. IM naloxone (4 studies)	• Response was greater with IM naloxone compared to IN naloxone (OR 2.6; 95% CI, 1.2 to 1.5; p=0.02) • TTR was faster with IM naloxone vs. IN naloxone. Median time to respond was 8 minutes for 2 mg IN naloxone. Studies showed response time to be 2.3 minutes to 9 minutes longer with the IN formulation compared to IM.	Moderate for all outcomes except hospitalizations

	• A second dose was given more often when IN naloxone was used. Of people given IN naloxone, 18.1% to 29% needed a second dose vs. 4.5% to 9.3% given IM naloxone. • No difference in hospitalization rates between routes • IM naloxone may be associated with more AE compared to IN (e.g., agitation, nausea or vomiting, headaches)	and adverse events which was low
IN naloxone vs. IV naloxone (4 studies)	• No difference in response • TTR was faster with IV naloxone • A second dose was needed more often with IN naloxone. Of people receiving an IN dose, 42%-44% required a second dose vs. 11%-20% in the IV group. • No difference in hospital length of stay • Hospital length of stay was similar between groups • IV naloxone was associated with more AE	Very low
IM naloxone vs. IV naloxone (1 study)	• No difference in response (measured at 5 minutes) • No results on repeat doses were available	Very low
Low-dose vs. high-dose naloxone (3 studies)	• High-dose naloxone (2 mg to > 0.15 mg) had a greater response than low dose naloxone (≤ 0.15 mg to 0.4 mg) • TTR was quicker in those received high dose naloxone (multiple routes) compared to low dose (mostly given IV) • A second dose of naloxone was more commonly needed in those receiving low dose naloxone (mixed routes) compared to high dose (mostly IV) • No difference was found in hospital admissions • High dose naloxone was associated with more adverse events (e.g., agitation, nausea, and vomiting)	Very low

Abbreviations: AE – adverse effects; CI – Confidence Interval; IM – intramuscular; IN – intranasal; IV – intravenous; OR – Odds Ratio; TTR – time-to-response

Limitations to the review are that most of the studies included administration of naloxone by a medical professional. None of the high-dose naloxone formulations recently approved by the FDA were studied (e.g., Kloxxado® 8 mg IN or Zimhi® 5 mg IM).[6]

CADTH – Administration of Naloxone in the Home or Community Setting

An updated CADTH review in 2019 evaluated the clinical effectiveness of the administration of naloxone in the home or community setting by non-health care professionals.[16] Six publications met inclusion criteria for the review; one systematic review, 2 guidelines, 2 non-randomized studies and one economic evaluation.[16] The evidence was considered low quality.

Take-home naloxone was associated with decreased mortality due to reductions in fatal overdoses.[16] Slightly lower rates in opioid overdoses were demonstrated in communities with take-home naloxone. There was limited evidence of reductions in emergency department visits in those patients that received take-home naloxone when prescribed an opioid. Guidelines recommend the use of naloxone in people who are likely to witness an opioid overdose, such as patients and their family members or care givers.[16] World Health Organization strongly recommends the use of any route of naloxone (e.g., IM, IN, IV, SQ) based on similar effectiveness data.[16] Naloxone is not recommended for pregnant women except in life-threatening situations.

After review, one systematic review was excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[17]

New Guidelines:

VA – Naloxone Rescue: Recommendations for Use

The VA published guidance on naloxone rescue in an effort to reduce the incidence of overdose amongst veterans.[18] The VA is required to offer opioid antagonists without requiring a copay. The IN naloxone formulations are preferred; however, the injection is available if contraindications to the IN formulation are present. The VA recommends the use of the Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD) to assess risk of opioid overdose. The Stratification Tool for Opioid Risk Mitigation (STORM) is also used to identify patients at risk of drug overdose or suicide. The following naloxone rescue recommendations are to be utilized for VA patients[18]:

- Assess risk of opioid-related adverse events
- Discuss naloxone rescue as a mitigation option with patients and care givers
- Offer naloxone to veterans prescribed opioids that are at increased risk
- Educate on opioid overdose prevention, recognition and response

Guidelines for Clinical Context:

ASAM – National Practice Guideline for the Treatment of Opioid Use Disorder

In 2020 the American Society of Addiction Medicine (ASAM) updated recommendation for OUD including the use of naloxone for opioid reversal.[19] A risk of bias evaluation and grading of the recommendations was not provided and authors had conflicts of interest, therefore, guidelines are included for clinical context. Guideline recommendations for the use of naloxone include[19]:

- Naloxone should be administered in the event of suspected opioid overdose
- Naloxone can be administered to pregnant women in case of overdose to save the mother's life
- Patients who are treated for OUD, and family members, should be given and instructed on the use of naloxone kits or prescription naloxone (OTC naloxone not available at time of guideline publication)
- First responders should be trained and authorized to carry naloxone

There is a lack of comparative efficacy studies between different routes of administration of naloxone.[19] Additional evidence is needed to inform the most effective strategies for opioid reversal.

New Formulations or Indications:

Naloxone (Narcan®): In March 2023, IN naloxone 4 mg received FDA approval to be changed from a prescription product to an OTC non-prescription product.[3] The switch was prompted by FDA soliciting safety and effectiveness data for naloxone products from manufacturers to allow the switch from prescription to OTC status to increase availability and access to naloxone.

Intranasal naloxone is a single-use, fixed-dose product approved for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression; for immediate administration as emergency therapy in settings where opioids may be present.[3] Naloxone rapidly reverses the effects of opioid overdose and this formulation may be used by those without medical training in community settings. The OTC naloxone formulation is indicated for neonates to adults.[3] The dose can be repeated every 2-3 minutes until emergency help arrives.

The FDA developed and validated a drug facts label (DFL) to ensure consumers could safely and effectively use the OTC naloxone. Pictures and corresponding wording allow for quick and clear directions for use.[20] No formulation changes were made to naloxone OTC compared to the prescription product and there was no new evidence presented to the FDA. Postmarketing safety results for the prescription IN naloxone were reviewed prior to OTC approval. Common adverse events include: increased blood pressure, constipation, toothache, and muscle spasms.

Nalmefene (Opvee®): A new IN formulation of nalmefene, previously available as an injectable, was approved in May of 2023.[15] The nalmefene nasal spray is an opioid antagonist indicated for the emergency treatment of known or suspected overdose caused by natural or synthetic opioids in adults and pediatrics 12 years and older.[15] Each nalmefene nasal spray delivers 2.7 mg into the nose. Nalmefene IN onset of action is 2.5 to 5 minutes.[15] Additional doses can be administered every 2-5 minutes if needed until emergency medical assistance arrives.

Nalmefene nasal spray approval was based on a study of healthy patients comparing the nalmefene nasal formulation to a single dose of nalmefene IM. There is pharmacokinetic and pharmacodynamic data that nalmefene has high affinity at μ-opioid receptors with a quick onset of action (0.250 hours to maximal concentration for IN nalmefene compared to 0.50 hours for IN naloxone) The half-life of nalmefene is 11.4 hours compared to a mean half-life for IN naloxone of 2.08 hours. There is no published direct comparative effectiveness data comparing IN nalmefene to IN naloxone.

The most common AEs are nasal discomfort, headache, nausea, dizziness, hot flush, vomiting, anxiety, fatigue, nasal congestion, throat irritation, rhinalgia, decreased appetite, dysgeusia, erythema, and hyperhidrosis.[15]

Naloxone (Zimhi®): A high-dose naloxone product, 5 mg IM or SQ in a single-dose prefilled syringe, was approved in October 2021 for use in pediatrics or adults or the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.[12] Approval was based on pharmacokinetic data from 14 healthy volunteers. Adverse events associated with high-dose naloxone include: nausea, dizziness, lightheadedness, and elevated bilirubin.

Naloxone (Kloxxado™): A high-dose (8 mg), single use IN naloxone was approved in April 2021 for pediatric and adult use.[11] This high-dose IN naloxone product 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. Emergency medical care should be sought after administration. Repeat does may be given every 2-3 minutes until arrival of emergency medical assistance.[11] The high-dose IN naloxone is designed for community or medical professional use. Approval was based off of the 505(b)(2) approval pathway under the Federal Food, Drug, and Cosmetic Act. This Act allows approval based on evidence from similar products. Pharmacokinetic data comparing IN naloxone to naloxone injection was used to demonstrate safety and efficacy.[21] Common adverse events associated with the use of high-dose IN naloxone are: abdominal pain, asthenia, dizziness, headache, nasal discomfort and presyncope.

Naloxone (Rextovy™): A 0.4 mg naloxone nasal formulation of naloxone was approved in March of 2023 for the use of 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.[13] This formulation was approved under the 505 (b)(2) approval pathway. Pharmacokinetic comparisons to naloxone 4 mg IN, naloxone 0.4 mg IM, naloxone 2 mg IV and naloxone 10 mg IN was used to support the approval of Rextovy™. Naloxone IN demonstrated higher concentrations than naloxone injections but lower than the IV formulation. Clinical data suggests similar safety profile as other naloxone products.[22]

Naloxone (ReVive™): A second OTC IN naloxone product was approved in July 2023.[10] The 3 mg single dose spray is approved for the emergency treatment of opioid overdose. Approval was based on pharmacokinetic comparisons to other naloxone products.

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Naloxone[23]	Narcan®	January 2017	Warnings and precautions	Naloxone 2 mg dose may prevent precipitation of severe opioid withdrawal in those with opioid dependence but may not provide an adequate and timely reversal if potent or very high doses of opioid have been taken.

Randomized Controlled Trials:
A total of 12 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

References:

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2. Food and Drug Administration. FDA Approval of First Over-the-Counter Naloxone Nasal Spray. FDA News Release. March 29, 2023. Accessed July 20, 2023.

3. Food and Drug Administration. Executive Summary - Narcan (naloxone hydrochloride) nasal spray, 4 mg. Integrated Review Template. Available at: fda.gov. Accessed July 23, 2023.

4. Britch SC, Walsh SL. Treatment of opioid overdose: current approaches and recent advances. *Psychopharmacology*. 2022;239(7):2063-2081. doi:10.1007/s00213-022-06125-5.

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6. Drug Effectiveness Review Project. Effectiveness and Harms of Naloxone for Opioid Overdose. June 2023.

7. Centers for Disease Control and Prevention. Increase in Fatal Drug Overdoses Across the United States Driven by Synthetic Opioids Before and During the COVID-19 Pandemic. CDC Health Alert Neetwork. December 17, 2020. Available at: https://emergency.cdc.gov/han/2020/han00438.asp. Accessed September 1, 2023.

8. Naloxone [prescribing information]. Richmond, VA; Kaleo, Inc. March 2023.

9. Narcan (naloxone) [prescribing information]. Plymouth Meeting, PA; Emergent Devices Inc. March 2023.

10. Rivive (naloxone) [prescribing information]. Bethesda, MD; Harm Reduction Therapeutics, Inc. June 30, 2023.

11. Kloxxado (naloxone) [prescribing information]. Columbus, OH: Hikma Specialty USA Inc. April 2021.

12. Zimhi (naloxone hydrochloride injection) [prescribing information]. San Diego, CA; Adamis Pharmaceuticals Corporation. October 2021.

13. Rextovy (naloxone) [prescribing information). So El Monte, CA; International Medication Systems, Limited. June 2023.

14. Nalmefene [Prescribing Information]. Stamford, CT: Purdue Pharma L.P. February 2022.

15. Opvee (nalmefene) [prescribing information]. Santa Monica, CA; Opiant Pharmaceuticals. May 2023.

16. Canadian Agency for Drugs and Technologies in Heatlh. Administration of Naloxone in a Home or Community Setting: A Review of the Clinical Effectiveness, Cost-Effectiveness and Guidelines. CADTH Rapid Repsonse Report: Summary with Critical Appraisal. December 18, 2019.

17. Dowling N, Merkouris S, Lubman D, et al. Pharmacological Interventions for the Treatment of Disordered and Problem Gambling. Cochrane Database of Systematic Reviews 2022; issue 9. Art. No. CD008936.

18. Veterans Affairs. Naloxone Rescue: Recommendations for Use. VA Pharmacy Benefits Managment Services, Medical Advisory Panel, and VISN Pharmacists Executives. February 2022.

19. ASAM Board of Directors. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder- 2020 Focused Update. American Society of Addiction Medicine. Available at: npg-jam-supplement.pdf. Accessed July 31, 2023.

20. Food and Drug Administration. Draft Labeling Review for Narcan (Naloxone Hydrochloride 4 mg) Nasal Spray. Labeling Review. 208411/S-006.

21. Food and Drug Administration. FDA Approves Higher Dosage of Naloxone Nasal Spray to Treat Opioid Overdose. April 30, 2021. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-higher-dosage-naloxone-nasal-spray-treat-opioid-overdose. Accessed August 1, 2023.

22. Food and Drug Administration. Naloxone (Rextovy). Center for Drug Evaluation and Research - Summary Review. June 29, 2023.

23. Food and Drug Administration. Narcan safety labeling changes. January 24, 2017. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=809. Accessed July 20, 2023.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
naloxone HCl	NALOXONE HCL	AMPUL	INJECTION	Y
naloxone HCl	NARCAN	AMPUL	INJECTION	Y
naloxone HCl	NALOXONE HCL	SYRINGE	INJECTION	Y
naloxone HCl	NALOXONE HCL	VIAL	INJECTION	Y
naloxone HCl	KLOXXADO	SPRAY	NASAL	Y
naloxone HCl	NALOXONE HCL	SPRAY	NASAL	Y
naloxone HCl	NARCAN	SPRAY	NASAL	Y
nalmefene HCl	NALMEFENE HCL	VIAL	INJECTION	N
naloxone HCl	NALOXONE HCL	AUTO INJCT	INJECTION	N
naloxone HCl	NALOXONE HCL	CARTRIDGE	INJECTION	N
naloxone HCl	ZIMHI	SYRINGE	INJECTION	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to July 17, 2023

Search Strategy:

#	Searches	Results
1	Naloxone/ or naloxone.mp.	29387
2	nalmefene.mp.	504
3	1 and 2	107
4	limit 3 to (english language and humans and yr="2016 -Current")	12

Appendix 3: Key Inclusion Criteria

Population	All individuals suspected of opioid overdose
Intervention	Naloxone or nalmefene
Comparator	Placebo or active treatment
Outcomes	Mortality, reversal of overdose symptoms, time- to-response, number needing a second dose, hospitalization, and adverse effects
Setting	Outpatient