# Naloxone Rescue: Recommendations for Use

## Naloxone Rescue for the VA Opioid Overdose Education and Naloxone Distribution (OEND) Program

March 2024

VA Pharmacy Benefits Management Services and National Formulary Committee in collaboration with

the VA National Harm Reduction Support & Development Workgroup

*The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. Local adjudication should be used until updated guidance and/or CFU are developed by the National PBM. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The drug Product Information should be consulted for detailed prescribing information.*

**Purpose:** Per VHA Undersecretary for Health's Information letter dated May 13, 2014, the VHA Pharmacy Benefits Management service will review and approve a recommendation for issuing naloxone kits for the VA Opioid Overdose Education and Naloxone Distribution (OEND) program. The recommendation document will also include guidance on identifying Veterans at risk of an opioid overdose.

## Recommendations and Information for Offering Naloxone Rescue:

***Overdose Education and Naloxone Distribution (OEND) should be offered to all patients that are at risk of an opioid overdose.***
Staff should: **Assess** the risk of opioid-related adverse events. **Educate** patients and caregivers on opioid overdose prevention, recognition, and response, including the proper use and storage of naloxone rescue medications. **Offer** naloxone rescue to Veterans prescribed or using opioids, including those who may be unknowingly exposed to opioids (e.g., illicit drugs/pills that may contain fentanyl), who are at increased risk for opioid overdose or whose provider deems, based on their clinical judgment, that the Veteran has an indication for readily available naloxone.

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<table>
<tr><th colspan="2">Examples of candidates recommended for OEND include (but not limited to):</th></tr>
<tr><td>Any active substance use disorder (does not include tobacco):<br>◊ Diagnosis of opioid use disorder (OUD)<br>◊ Diagnosis of stimulant use disorder (e.g., amphetamines, cocaine)</td><td>Prescribed Opioids:<br>• >50 MEDD<br>• Long acting or extended-release formulations (e.g., morphine SA, fentanyl)<br>• Concomitant use of CNS depressants<br>◊ Identified as very-high risk per VHA's Stratification Tool for Opioid Risk Mitigation (STORM)</td></tr>
<tr><td>◊ Veterans with and opioid or stimulant overdose in the past year</td><td>Use of illicit or non-prescribed substances that could contain opioids</td></tr>
<tr><td rowspan="3">Loss of tolerance and/or at risk of non-prescribed use:<br>• During and after a recently completed opioid taper<br>• After detoxification/withdrawal treatment, residential treatment, or any period of abstinence<br>• Recent incarceration or release from a protected environment</td><td>Higher risk for suicide/overdose based on predictive modeling tools (e.g., STORM, RIOSORD, see links in key resource section below)</td></tr>
<tr><td>Prescriber determines individual is at risk of a potential overdose</td></tr>
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<tr><td colspan="2">◊ VHA safety initiatives to promote OEND; Veterans in above identified risk groups are part of the OEND2, OEND3, OEND4 and OEND5 metrics OEND SharePoint</td></tr>
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**Veterans who do NOT routinely need to be offered naloxone rescue**:

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|---|---|
| **TRAMADOL** | Tramadol has a mu opioid receptor affinity approximately 6,000-fold less than morphine and pharmacologic evidence suggests a non-opioid mechanism of action, a lack of naloxone reversibility of its analgesic effect, and lack of significant naloxone-induced withdrawal.[1] Additionally, naloxone may increase the risk of seizures when administered in the context of a tramadol overdose.[2] Thus, while most low risk patients on single agent tramadol may not warrant a naloxone prescription, high risk patient (see table above) are candidates for naloxone. It is recommended to provide patients prescribed tramadol with overdose education to ensure that they are aware of risks associated with concomitant use of tramadol and opioids and understand the means available to reduce overdose risk. |
| **HOSPICE** | OEND is not routinely used in patients who have comfort-oriented goals receiving opioids to reduce suffering toward the end of life (i.e., hospice patients). The signs and symptoms of life-threatening opioid overdose overlap with and may be mistaken for the common signs and symptoms of the dying process. Family members of Veterans in hospice programs who receive OEND training should simultaneously receive education about the overlap in signs and symptoms with the dying process. OEND may be considered for those under hospice care with clinical consideration including (but not necessarily limited to) the patient's clinical conditions (including medical, mental health, and substance use disorder comorbidities), prognosis, goals of care, home environment, opioid dose and prior opioid history |

## Prescribing of Naloxone products: *To facilitate implementation of OEND, VHA has created an "Overdose Education and Naloxone" CPRS note and "Naloxone Overdose Education" Oracle Powerform to facilitate the education and order process* †

- The nasal preparations of naloxone are the preferred national formulary products; however, the naloxone IM kit and IM injection are available on the national formulary for those patients who have contraindications to the nasal products*
- Naloxone requires a prescription but will be provided to any Veteran enrolled in VHA care at a zero copay.[3]
- Each prescription order contains 2 dose units of naloxone.
- Prescriptions should be processed with a 1-day supply and marked with at least one refill.
- Standing orders may be utilized, but the overdose education, and agreement of the Veteran to receive a naloxone prescription, should occur before naloxone dispensation.
- Reassessment of the need for OEND should occur at least annually.
- Documentation within the "Overdose Education and Naloxone" CPRS note or "Naloxone and Overdose Education" Oracle Powerform should occur whether Veteran accepts a naloxone rescue device, declines such, or reports having in-date product on hand (e.g. for in-date product, providers should document "has current naloxone (i.e., not used and not expired)" [1]

## Prescribing of other naloxone rescue products besides the 4mg nasal spray

- For patients with a contraindication to nasal administration: IM kits or devices are available
- *For patients for whom there may be a concern that a higher dose of naloxone may be required for reversal the 8mg naloxone nasal spray (KLOXXADO) is on formulary
- *For patients for whom there is a concern that a higher potency opioid antagonist may be beneficial or in the rare case of true naloxone allergy, nalmefene (OPVEE) is FDA approved. Although not on VA formulary, can be accessed via routine non-formulary request processes

*NOTE Although Naloxone 8mg nasal spray, 5mg IM injection, and nalmefene nasal spray provide higher plasma levels or longer half-life, respectively, clinical trials to date do not exist to suggest a difference in real world reversal rates. Recent reports in peer reviewed journals have not reported an association between increasing rates of illicit fentanyl in the community, fentanyl concentrations in vivo and a corresponding increase in dose of naloxone needed for reversal.[5-7] **Use shared decision making in determining if a higher dose/potency opioid antagonist device should be prescribed.**

## Documentation of Overdose Events or Naloxone Rescue Use†

- Per VHA Directive 1160.04 VHA Programs for Veterans with Substance use Disorders, all overdoses occurring within the past 12 months are required to be reported using national standardized documentation (e.g., Suicidal Behavior and Overdose Report CPRS note template or Oracle Powerform.
- If the Naloxone Rescue device was used on someone other than the Veteran, the Naloxone Use Note should be used.

## Product Information

**Efficacy**: Naloxone produces virtually no pharmacologic effects in patients not taking opioids. Onset of action is less than 2 minutes when naloxone is administered intravenously (IV) to adults. IV has a faster onset than intranasal (IN) administration when time from dose administration to clinical response is measured, but there is no time difference when measuring the time from patient contact to clinical response due to the time required to establish an IV access. Time to clinical response is similar for IM and IN routes when a concentration of at least 2mg/ml is utilized for nasal administration.[8]
**Safety**: Naloxone has a low risk of side effects; the most common stem from opioid withdrawal in persons who have a physical dependence.

**Table 1 – Naloxone Rescue Device Comparison**

| *All products are FDA-approved forms of naloxone that the FDA states can be considered as options for community distribution. The nasal spray devices were specifically designed for layperson use (e.g., includes instructions for use) and no assembly is required.* | **Nasal Spray (4 mg) (Preferred Naloxone Formulation)** | **Nasal Spray (8 mg)** | **Injectable IM (0.4mg) generic** | **Injection (5 mg/0.5ml)** |
|---|---|---|---|---|
| |  |  |  |  |
| ***Trade name*** | Narcan | Kloxxado | Not applicable | Zimhi |
| ***Strength*** | 4 mg/0.1ml x<br>2 dose units | 8 mg/0.1ml x<br>2 dose units | IM: 0.4 mg/ml x<br>2 vials supplied | 5 mg/0.5ml x<br>2 dose units |

†Examples of CPRS note templates and Oracle Powerforms can be found at OEND CPRS Products.pptx (sharepoint.com)

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|---|---|---|---|---|
| ***Assembly*** | None required | None required | Remove cap from naloxone vial, uncover needle; insert thru rubber plug of upside down vial. Pull back on plunger to 1ml. | None required |
| ***Dosing*** [a] | Spray 0.1ml into one nostril; repeat with second device into other nostril after 2-3 minutes if no/minimal response | Spray 0.1ml into one nostril; repeat with Second device into other nostril after 2-3 minutes if no/minimal response | IM: Inject 1ml(0.4mg) at 90 angle into large muscle (upper arm, thigh, outer buttock). Give another dose if no reaction or if breathing stops again | Administer the initial dose intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary, and repeat after 2-3 minutes if no or minimal response |
| ***Administration.*** Instruct the patient or caregiver to read the *Instructions for Use* at the time they receive a prescription for naloxone. | 1. Place the person on their back<br>2. Hold the nasal spray with thumb on the bottom of the plunger and our firs and middle fingers on either side of the nozzle<br>3. Gently insert the tip of the nozzle into one nostril until fingers on either side of the nozzle are against the bottom of the person's nose.<br>4. Press the plunger firmly to give the dose of naloxone<br>5. Remove the nasal spray from the nostril after giving the dose<br>6. Get emergency medical help (call 911)<br>7. If required give another dose in the other nostril using a new nasal spray<br>8. If the person is breathing normally, turn the patient on their side (recovery position) after giving naloxone | 1. Place the person on their back<br>2. Hold the nasal spray with thumb on the bottom of the plunger and first and middle fingers on either side of the nozzle<br>3. Gently insert the tip of the nozzle into one nostril until fingers on either side of the nozzle are against the bottom of the person's nose.<br>4. Press the plunger firmly to give the dose of naloxone<br>5. Remove the nasal spray from the nostril after giving the dose<br>6. Get emergency medical help (call 911)<br>7. If required give another dose in the other nostril using a new nasal spray<br>8. If the person is breathing normally, turn the patient on their side (recovery position) after giving naloxone | 1. Place the patient on their back<br>2. Remove cap from naloxone vial and uncover the needle<br>3. Insert needle through rubber plug with vial upside down<br>4. Pull back on plunger and pull down to 1 ml<br>5. Inject 1 ml of naloxone at a 90º angle into a large muscle (upper arm/thigh or outer buttocks)<br>6. Get emergency medical help (call 911)<br>7. If required, give another dose using a new needle and vial of naloxone<br>8. If the person is breathing normally, turn tonto side (recovery position) after giving naloxone<br>9. NEEDLE DISPOSAL – deposit used syringe in a biohazard sharps container | 1. Place the person on their back<br>2. Remove the needle cap<br>3. Inject into outer thigh and push the plunger all the way down until it clicks and hold for 2 seconds<br>4. After use, slide the safety guard over the needle. Put the used syringe into the blue case and close the case.<br>5. Get emergency medical help (call 911)<br>6. If required, give another dose using a new prefilled syringe.<br>7. If the person is breathing normally, turn onto side (recovery position) after giving naloxone<br>8. NEEDLE DISPOSAL – Pull safety guard down over needle, place used device back in original blue box and give to healthcare/EMS provider for disposal |
| ***Pharmacokinetics***<br>• **Dose/route**<br>• **T1/2 (h)**<br>• **Tmax (h)**<br>• **Cmax (ng/ml)**<br>• **AUC0-inf (ng□h/ml)**<br>• **Bioavailability (%)**[c] | 4 mg IN[b]<br>2.08<br>0.50<br>4.83<br>7.95<br>44.2% | 8mg IN<br>1.76-2.69<br>0.25<br>12.3-12.8<br>16.7-19.0<br>41.6-47.0% | 0.4mg IM<br>1.24<br>0.38<br>0.88<br>1.76<br>100% | 5mg IM/SQ<br>1.50<br>0.25<br>17.2<br>26.6<br>100% |
| ***Usability*** | Successful use of the 4mg NS was observed in 90.5% of users without training.[d] All forms are FDA approved options for community distribution and use by individuals with or without medical training to stop or reverse the effects of an opioid overdose.[9] | | | Usability study reported a 100% successful completion of all steps needed to use the device among untrained adolescents.[10] |

**a** Response = return of spontaneous respirations to rate ≥ 10 breaths/minute. **b** All values listed for naloxone spray 4mg are geometric mean values, Tmax reported as median. **c** Relative bioavailability listed for naloxone NS and Injection is relative to IM-administered product. **d** Successful use = correct performance of two critical tasks: 1) insertion of the nozzle of the spray applicator into the nostril and 2) correct use of the plunger

## Key Resources

- **Education (Patient and Provider) –**
  VHA National Academic Detailing service has multiple provider and Veteran discussion guides to facilitate discussions about Naloxone Rescue VHA Academic Detailing OEND sharepoint

- **Policies/Directives, Implementation Resources, Community of Practice and Documents Library**
  Can be found at Opioid Overdose Education and Naloxone Distribution (OEND) (sharepoint.com)
- The national Substance Abuse and Mental Health Services Administration (SAMHSA) has published a recently updated SAMHSA 2024 Overdose Prevention and Response Toollkit

- **Population Management and Risk Assessment Tools**
  The OEND Dashboard provides VISN and Facility patient-level detail of actionable, at-risk Veterans. Both the VA Stratification Tool for Opioid Risk Mitigation STORM and VA's Opioid Therapy Risk Report OTRR include predictive model estimates for the likelihood of overdose or suicide or serous opioid-related adverse event in the next 1-3 years and can facilitate shared decision-making regarding need for a naloxone rescue device.

## Additional Information

- **Xylazine –** Reports from DEA that xylazine mixed with illicit drugs has been detected and increasing in every region of the US.[11] Co-intoxication with opioids containing xylazine can lead to a profound sedation that is not reversed by opioid antagonist administration. Rescue breathing is an additional intervention that has been recommended but Naloxone/Opioid Antagonist administration and engaging emergency medical services are still the key priority interventions given that the majority of xylazine deaths involve opioids. VHA Academic Detailing VHA AD - Xylazine: What clinicians need to Know and CDC information resource What You Should Know About Xylazine | Drug Overdose | CDC Injury Center are linked.
- **Rapid Naloxone Initiative –** Information regarding storage of a naloxone rescue device in an Automated External Defibrillator (AED) cabinet or equipping VA police may be found at VHA Rapid Naloxone Initiative - Implementation Toolkit
- **Shelf-Life Extension --** The FDA in Feb 2024 announced a shelf life extension of up to 4 years for Naloxone (Narcan) 4mg nasal spray.[4] However, VHA clinical reminders alert annually and represent a best practice to reassess Veteran ongoing risks, need for, and access to naloxone rescue on at least a yearly basis. OEND sharepoint[2]

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