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# The Medical Letter®

## on Drugs and Therapeutics

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### IN BRIEF

## Higher-Dose Naloxone Nasal Spray (*Kloxxado*) for Opioid Overdose

The FDA has approved a higher-dose intranasal naloxone formulation (*Kloxxado* – Hikma) for emergency treatment of opioid overdose. A single spray of the new formulation delivers 8 mg of naloxone; a formulation that delivers 4 mg per spray (*Narcan*) was approved in 2015.<sup>1</sup>

#### Pronunciation Key

*Kloxxado*: kloks ah' doh

Opioid-related overdose deaths have been increasing in the US and this increase has accelerated during the COVID-19 pandemic.<sup>2</sup> Studies of Emergency Medical Services calls for opioid overdose during the pandemic have found an increase in patients receiving multiple doses of naloxone.<sup>3</sup> The US Department of Health and Human Services has published recommendations for prescribing or co-prescribing naloxone for individuals who are at risk of opioid overdose (see Table 1).<sup>4,5</sup>

No clinical data are available on when to use a higher dose of naloxone for reversal of an opioid overdose. A higher dose may be required when the overdose is due to use of illicitly manufactured synthetic opioids such as fentanyl and its analogs, or when it is more severe or has progressed.

**CLINICAL STUDIES** – No new clinical trials were required for FDA approval of the 8-mg formulation. Two unpublished pharmacokinetic studies (summarized in the package insert) in healthy adults compared a single 8-mg intranasal dose of naloxone to single doses of the drug given IM (0.4 mg) and IV (2 mg). The median time to reach maximum serum concentrations (T<sub>max</sub>) was about 15 minutes with both intranasal and IM administration. The mean maximum naloxone serum concentration following intranasal administration was about 10 times higher than that

Table 1. Persons Who Should Carry Naloxone<sup>1,2</sup>

#### Patients prescribed opioids who:

- ▶ Are receiving a dosage  $\geq 50$  morphine milligram equivalents (MME) per day
- ▶ Have respiratory conditions such as chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea (regardless of opioid dose)
- ▶ Have been prescribed benzodiazepines (regardless of opioid dose)
- ▶ Have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (regardless of opioid dose)

#### Patients at high risk for an opioid overdose, including those:

- ▶ Using heroin or illicit synthetic opioids or misusing prescription opioids
- ▶ Using other illicit drugs such as methamphetamine or cocaine that could potentially be contaminated with illicit synthetic opioids like fentanyl
- ▶ Receiving treatment for opioid use disorder, including medication-assisted treatment with methadone, buprenorphine, or naltrexone
- ▶ With a history of opioid misuse who were recently released from incarceration or other controlled settings and are no longer tolerant to opioids

1. HHS. Naloxone: the opioid reversal drug that saves lives. Available at: <https://bit.ly/3k68NiV>. Accessed August 26, 2021.

2. Includes at-risk individuals, their caregivers, and those likely to respond to an overdose event.

achieved after IM administration. The IV dose had a faster onset of action than the intranasal dose, but after about 10 minutes, serum concentrations were higher with the nasal spray.

**ADVERSE EFFECTS** – Naloxone can precipitate acute withdrawal symptoms in opioid-dependent patients; the risk may be greater with higher doses. Acute opioid withdrawal is associated with anxiety, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, and abdominal or muscle cramps. Naloxone-induced noncardiogenic pulmonary edema has been reported rarely and appears to be more common when higher doses are used.<sup>6</sup>

In the two pharmacokinetic studies in healthy adults, abdominal pain, asthenia, dizziness, headache, nasal discomfort, and presyncope were reported in a few of the subjects who received intranasal naloxone 8 mg. Signs of nasal inflammation and nasal congestion were also observed.

Table 2. *Kloxxado* vs *Narcan*

	<i>Kloxxado</i>	<i>Narcan</i>
Formulation	8 mg/0.1 mL nasal spray	4 mg/0.1 mL nasal spray
Dosage <sup>1</sup>	8 mg intranasally	4 mg intranasally
Tmax	15 minutes	30 minutes
Cmax	12.3-12.8 ng/mL	4.8 ng/mL
Half-life	1.8-2.7 hours	2.1 hours
Cost <sup>2</sup>	\$62.50 <sup>3</sup>	\$62.50 <sup>4</sup>

1. Dose can be repeated every 2-3 minutes until the patient responds or emergency medical personnel arrive.
2. Approximate WAC for 1 nasal spray device (supplied in cartons containing 2 devices). WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. August 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. [www.fdbhealth.com/policies/drug-pricing-policy](http://www.fdbhealth.com/policies/drug-pricing-policy).
3. Community organizations and first responders can place bulk orders for *Kloxxado* with the manufacturer.
4. *Narcan* is available from the manufacturer at a discounted price of \$37.50 per 4 mg nasal spray device to law enforcement, firefighters, first responders, departments of health, local school districts, colleges and universities, and community-based organizations.

**PREGNANCY** – No embryotoxic or teratogenic effects occurred in pregnant mice and rats treated with large doses of naloxone. Naloxone crosses the placenta; it may induce preterm labor and cause opioid withdrawal symptoms in the fetus of an opioid-dependent mother.

**DOSAGE AND ADMINISTRATION** – *Kloxxado* is supplied in cartons containing two 8 mg/0.1 mL single-use nasal spray devices. The recommended dosage for adults and children is 8 mg administered as a single spray into one nostril. Additional doses can be given every 2 to 3 minutes in alternating nostrils using a new device for each dose. No assembly or priming of the device is required.

**AVAILABILITY** – Every state in the US now has a naloxone access law that allows an individual to obtain naloxone without a personal prescription. These laws may also grant civil and criminal immunity to laypersons who administer naloxone and to healthcare professionals who prescribe or dispense the drug to laypersons. ■

1. Naloxone (Narcan) nasal spray for opioid overdose. *Med Lett Drugs Ther* 2016; 58:1.
2. CDC. Health Alert Network (HAN). Increase in fatal drug overdoses across the United States driven by synthetic opioids before and during the COVID-19 pandemic. December 17, 2020. Available at: <https://bit.ly/3AU8nCZ>. Accessed August 26, 2021.
3. D Khoury et al. Increases in naloxone administrations by emergency medical services providers during the COVID-19 pandemic: retrospective time series study. *JMIR Public Health Surveill* 2021; 7:e29298.
4. HHS. Naloxone: the opioid reversal drug that saves lives. Available at: <https://bit.ly/3k68NiV>. Accessed August 26, 2021.
5. Drugs for opioid use disorder. *Med Lett Drugs Ther* 2017; 59:89.
6. S Elkattawy et al. Naloxone induced pulmonary edema. *J Community Hosp Intern Med Perspect* 2021; 11:139.

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