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# The Medical Letter®

## on Drugs and Therapeutics

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### ▶ **Zimhi – A Higher-Dose Injectable Naloxone for Opioid Overdose**

The FDA has approved a higher-dose injectable formulation of the opioid antagonist naloxone (*Zimhi* – Adamis) for emergency treatment of opioid overdose. A single IM or SC injection of the new formulation delivers 5 mg of naloxone; injectable formulations that deliver 0.4 mg or 2 mg of the drug have been available for years. Naloxone is also available in intranasal formulations for the same indication (see Table 1).<sup>1,2</sup>

#### Pronunciation Key

*Zimhi*: zim' hye

**HIGH-DOSE NALOXONE** – The rationale for the new 5-mg IM/SC formulation of naloxone is that higher doses of injectable naloxone may be needed to reverse opioid overdoses due to potent synthetic opioids such as fentanyl; whether higher doses of the drug are more effective than lower doses in such cases remains to be established. Higher doses can increase the risk of naloxone-induced opioid withdrawal and acute respiratory distress syndrome.

**CLINICAL STUDIES** – No new clinical trials were required for FDA approval of *Zimhi*. Approval was based on the results of pharmacokinetic studies in healthy adults showing that systemic exposure was significantly higher with a single 5-mg IM dose of the new formulation than with a single 2-mg IM dose of naloxone.<sup>3,4</sup>

**ADVERSE EFFECTS** – Use of *Zimhi* in healthy subjects was associated with nausea, dizziness, lightheadedness, and increases in serum bilirubin levels.

Naloxone can precipitate acute withdrawal in opioid-dependent patients; the risk is greater with higher doses. Symptoms of acute opioid withdrawal include anxiety, agitation, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting (which can lead to aspiration), diarrhea, abdominal and muscle cramps, tachycardia, and hyperten-

Table 1. Some Naloxone Formulations

Drug	Formulations <sup>1</sup>	Usual Dosage	Cost <sup>2</sup>
<b>Parenteral</b>			
generic	0.4 mg/mL vials and syringes; 2 mg/2 mL syringes	0.4-2 mg IV, IM, or SC <sup>3</sup>	\$13.70 <sup>4</sup>
<i>Zimhi</i> (Adamis)	5 mg/0.5 mL syringes	5 mg IM or SC <sup>5</sup>	62.50
<b>Intranasal</b>			
generic	4 mg/0.1 mL spray	4 mg intranasally <sup>6</sup>	54.00 <sup>6</sup>
<i>Narcan</i> (Emergent)	4 mg/0.1 mL spray	4 mg intranasally <sup>6</sup>	62.50 <sup>6,7</sup>
<i>Kloxxado</i> (Hikma)	8 mg/0.1 mL spray	8 mg intranasally <sup>6</sup>	62.50 <sup>6,8</sup>

1. A 10-mg auto-injector is available for military use in situations where use of high-potency opioids as chemical weapons is suspected.
2. Approximate WAC for one dose. 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. March 5, 2022. Reprinted with permission by First Databank, Inc. All rights reserved. ©2022. [www.fdbhealth.com/drug-pricing-policy](http://www.fdbhealth.com/drug-pricing-policy).
3. Dose can be repeated every 2-3 minutes up to a total of 10 mg.
4. Cost of a 1-mL vial.
5. Dose can be repeated every 2-3 minutes until the patient responds or emergency medical personnel arrive.
6. Supplied in cartons containing two nasal spray devices.
7. Available from the manufacturer at a discounted price of \$37.50 per 4-mg nasal spray device to law enforcement, firefighters, other first responders, departments of health, local school districts, colleges and universities, and community-based organizations.
8. Community organizations and first responders can place bulk orders with the manufacturer.

sion. Serious effects of acute opioid withdrawal, including pulmonary edema, cardiac arrhythmia, and cardiac arrest, occur rarely. Naloxone-induced noncardiogenic pulmonary edema has been reported rarely and may be more common when higher doses are used.<sup>5</sup>

**DOSAGE AND ADMINISTRATION** – The recommended dosage of *Zimhi* is 5 mg administered IM or SC; additional doses can be given every 2 to 3 minutes until the patient responds or emergency medical personnel arrive.

**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.

**CONCLUSION** – *Zimhi*, a 5-mg injectable formulation of the opioid antagonist naloxone, has been approved by the FDA for treatment of opioid overdose. No clinical data are available on when to use this higher dose of the drug. Higher doses can increase the risk of acute opioid withdrawal in opioid-dependent patients. ■

1. Drugs for opioid use disorder. *Med Lett Drugs Ther* 2017; 59:89.
2. In brief: Higher-dose naloxone nasal spray (Kloxxado) for opioid overdose. *Med Lett Drugs Ther* 2021; 63:151.
3. RB Moss et al. An open-label, randomized, single-dose, two-period, two-treatment crossover bioavailability study comparing 5 mg/0.5 mL of intramuscular naloxone hydrochloride to 2 mg/0.4 mL intramuscular naloxone hydrochloride autoinjector in healthy subjects. *J Opioid Manag* 2020; 16:209.
4. RB Moss et al. Comparative pharmacokinetic analysis of community use naloxone formulations for acute treatment of opioid overdose. *J Addict Behav* 2019 November 7 (epub).
5. S Elkattawy et al. Naloxone induced pulmonary edema. *J Community Hosp Intern Med Perspect* 2021; 11:139.

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