

New Dosage Form: Nalmefene Nasal Spray (OpveeTM)

FDA approved June 2023

Opiant / Indivior Pharmaceuticals Inc.

Indications: Nalmefene nasal spray is indicated for the emergency treatment of known or suspected overdose caused by natural or synthetic opioids in individuals aged 12 and above, characterized by respiratory or CNS depression. It's meant for immediate use in emergencies where opioids might be involved but is not a replacement for emergency medical care.

Mechanism of action

- Nalmefene acts as a selective opioid receptor antagonist, targeting the mu & delta receptors, and partially affecting the kappa receptor. It's thought to reduce alcohol consumption by influencing cortico-mesolimbic function.
- Reverses the effects of natural or synthetic opioids, including respiratory depression, sedation, and hypotension

Dosage & Administration

Opvee[®] nasal spray	Strength	2.7 mg/0.1 mL
	Administration	<ul style="list-style-type: none">• Administer a single spray (0.1ml) into one nostril. Use a new spray with each dose, repeating every 2-5 minutes if there's no response or if pt responds but relapses into respiratory depression, until medical assistance is available.• Additional supportive & resuscitative measures can be beneficial while awaiting emergency medical help.
Narcan[®] nasal spray	Strength	4 mg/0.1ml Total volume of 2-unit package: 8 mg/0.2ml; each Rx order contains 2 dose units of naloxone
	Administration	<ul style="list-style-type: none">• Spray 0.1ml into one nostril; repeat with second device into alternate nostril after 2-3 minutes if no or minimal response.• Additional doses may be required until medical assistance available.• Do not prime or test the device prior to administration.
Kloxxado[®] nasal spray	Strength	8 mg/0.1ml Single dose intranasal spray containing 8mg of naloxone HCL in 0.1ml; Each carton contains (2) 8 mg nasal spray devices.
	Administration	<ul style="list-style-type: none">• Administer a single spray intranasally into one nostril. Re-administer KloxxadoTM using a new nasal spray every 2 to 3 minutes, if patient does not respond or responds and then relapses into respiratory depression.• Additional doses may be necessary until emergency medical assistance becomes available.• Administer in alternate nostrils with each dose.• Do not prime or test the device prior to administration

Dose Adjustments

Risk of Limited Efficacy	<ul style="list-style-type: none">• Reversal of respiratory depression by partial agonists or mixed agonist/antagonists (ex. buprenorphine and pentazocine) may be incomplete.• May require higher or repeat naloxone doses
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Adverse Effects

Most common adverse effects (incidence at least 2%)	Nasal discomfort, headache, nausea, dizziness, hot flush, vomiting, anxiety, fatigue, nasal congestion, throat irritation, rhinalgia, reduced appetite, dysgeusia, erythema, & hyperhidrosis
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Pharmacokinetics

	IN Naloxone	IN 2.7 mg Nalmefene
Onset	5 to 20 minutes (with range of doses)	2.5 to 5 minutes Full recovery of respiratory drive: 5 to 15 minutes
Tmax	0.25 to 0.5 hours	0.25 to 0.267 hours
Bioavailability	41.6% to 54% relative to IM	0.81 relative to IM
Half life	1.76 to 2.69 hours	10.8 to 12.5 hours
Metabolism	Hepatic (extensive)	Hepatic (extensive)
Excretion	Renal: 70% (in 72 hours)	Renal (~59%), Fecal (17%)

Warnings & Precautions

- Risk of recurrent respiratory and CNS depression
- Risk of limited efficacy with partial agonists or mixed agonist/antagonists
- Precipitation of severe opioid withdrawal
- Risk of cardiovascular effects
- Risk of opioid overdose from attempts to overcome the blockade



Role in Therapy

- Nalmefene IN, an innovative prescription nasal spray, combines an extended duration of effect with rapid overdose reversal
 - new dosage form for treatment of known or suspected opioid overdose
 - was previously available only as an injection
- Approved by the FDA in May this year with priority review, nalmefene IN is scheduled to launch in Q4 of 2023
 - developed through funding from the Biomedical Advanced Research & Development Authority to address opioid overdose reversal and counter synthetic opioid chemical attacks
- While its potential for prolonged withdrawal symptoms presents challenges, its benefits in scenarios involving synthetic opioids highlight its relevance in the evolving opioid crisis

- As nalmefene IN becomes part of the toolkit available, it has the potential to contribute to saving lives and supporting individuals along the path to opioid addiction recovery
- Naloxone offers an alternative for opioid overdose management, with choices between nasal and injectable forms
 - In March 2023, FDA approved the first naloxone OTC product (Narcan 4 mg/mL nasal spray). Information regarding availability & pricing has not been announced.
 - Both Opree and naloxone exhibit comparable safety profiles
 - Naloxone products are prescribed for both adult and pediatric patients, whereas Opree is indicated for individuals aged 12 and older
 - Nalmefene nasal spray, resembles and functions like naloxone IN, and provides an alternative option for reversing opioid overdose, particularly within the context of evolving opioid crisis
 - While working similarly to naloxone, Nalmefene's extended effects bring both opportunities and complexities to overdose reversal
 - Opioid receptor binding studies have shown nalmefene's higher acute potency than naloxone in reversing opioid effects at mu & kappa receptors. However, in a well-designed study comparing both drugs in healthy volunteers receiving continuous opioid infusion, their efficacy in reversing respiratory depression was comparable.
 - Nalmefene's longer elimination half-life led to prolonged duration of opioid reversal action
 - Nalmefene and naloxone had equal efficacy in managing suspected narcotic overdose in an emergency setting
 - Extended Duration of Action
 - IN nalmefene's distinguishing feature is its longer-acting effect compared to naloxone
 - IV nalmefene's duration of action is significantly longer than that of naloxone at doses of 0.3 mg or higher
 - extended duration of action can be advantageous in scenarios where fentanyl or other synthetic opioids are involved
 - Fentanyl's prolonged presence in the body may require multiple doses of naloxone over several hours to ensure complete reversal. Nalmefene's longer duration could provide sustained protection against relapse during this critical period
 - Potential Downsides due to longer-acting effect of nalmefene
 - Users may experience withdrawal symptoms, including nausea, diarrhea, muscle cramps, & anxiety. These symptoms might persist for 6 hours or longer requiring additional management / treatment
 - In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. Monitor for the development of opioid withdrawal.
 - This contrast with naloxone's relatively shorter withdrawal symptoms has raised concerns among some experts
 - Opportunity to be integrated into comprehensive treatment strategies for opioid addiction
 - offers a longer window of protection against relapse
 - offer an advantage in supporting individuals during the critical moments following an overdose
- Caution for recurrent respiratory and CNS depression
 - While nalmefene's duration of action is as long as most opioids, there's potential for recurrent respiratory depression. Monitor closely and administer repeat doses using a new spray if needed, while awaiting emergency assistance.

- Limited Efficacy for Partial Agonists Mixed Agonist/Antagonists
 - Reversal of respiratory depression induced by partial agonists or mixed agonists/antagonists (such as buprenorphine), may be incomplete. Larger or repeat doses could be necessary.
 - Risk of Overdose from Overcoming Blockade: Trying to counter opioid withdrawal by using high or repeated doses of opioids can result in opioid intoxication and fatal outcomes.

Availability and Cost

- Approved for patients 12 and older, requires prescription.
- Potential to become an essential tool for healthcare providers, first responders, and caregivers
- Anticipated availability and pricing in 4th quarter, 2023

Cost Comparison

Drug and Manufacturer	Dosage Forms & Strength	Dosing Regimen	Cost per Dose
Opree (nalmefene) [Opant Pharmaceuticals Inc.]	• Single-use nasal spray: 2.7 mg/0.1 mL	• Administer a single spray into one nostril. If needed, administer additional doses every 2 to 5 minutes until emergency medical assistance arrives.	\$97.00
Kloxxado (naloxone hydrochloride) [Hikma Pharmaceuticals USA Inc.]	• Single-use nasal spray: 8 mg/0.1 mL	• Administer a single spray into one nostril. If needed, administer additional doses every 2 to 3 minutes until emergency medical assistance arrives.	\$75.00
Narcan (naloxone hydrochloride) [Various]	• Single-use nasal spray: 4 mg/0.1 mL		Brand: \$75.00 Generic: \$54.00 OTC: \$50.00

Formulary Recommendation

- In light of the opioid epidemic and the need to make all reversal tools accessible, recommend adding to the formulary for BHRS, CareAdvantage, and HealthWorx for age 12 and older without restrictions

References

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