

# OPVEE- nalmefene hydrochloride spray

## Indivior Inc.

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### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPVEE® safely and effectively. See full prescribing information for OPVEE.

**OPVEE® (nalmefene) nasal spray**  
**Initial U.S. Approval: 1995**

### INDICATIONS AND USAGE

OPVEE nasal spray is an opioid antagonist indicated for the emergency treatment of known or suspected overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression. (1)

OPVEE nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present. (1)

OPVEE nasal spray is not a substitute for emergency medical care. (1)

### DOSAGE AND ADMINISTRATION

- OPVEE nasal spray is for intranasal use only (2.1)
- Seek emergency care immediately after use (2.1)
- Administer a single spray of OPVEE nasal spray intranasally into nose. (2.2)
- Administer additional doses of OPVEE nasal spray, using a new nasal spray with each dose, if the patient does not respond or responds and then relapses into respiratory depression, additional doses of OPVEE nasal spray may be given every 2 to 5 minutes until emergency medical assistance arrives. (2.2)
- Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance. (2.2)

### DOSAGE FORMS AND STRENGTHS

Nasal spray: 2.7 mg of nalmefene in 0.1 mL (3)

### CONTRAINDICATIONS

Hypersensitivity to nalmefene or to any of the other ingredients. (4)

### WARNINGS AND PRECAUTIONS

- Risk of Recurrent Respiratory and Central Nervous System Depression: While the duration of action of nalmefene is as long as most opioids, a recurrence of respiratory depression is possible, therefore, keep patient under continued surveillance and administer repeat doses of OPVEE using a new nasal spray with each dose, as necessary, while awaiting emergency medical assistance (5.1)
- Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists: Reversal of respiratory depression caused by partial agonists or mixed agonists/antagonists, such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses may be required. (5.2)
- Precipitation of Severe Opioid Withdrawal: Use in patients who are opioid dependent may precipitate opioid withdrawal. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. Monitor for the development of opioid withdrawal. (5.3)
- Risk of Cardiovascular (CV) Effects: Abrupt postoperative reversal of opioid depression may result in adverse CV effects. These events have primarily occurred in patients who had preexisting CV disorders or received other drugs that may have similar adverse CV effects. Monitor these patients closely in an appropriate healthcare setting after use of nalmefene hydrochloride. (5.3)
- Risk of Opioid Overdose from Attempts to Overcome the Blockade: Attempts to overcome opioid withdrawal symptoms caused by opioid antagonists with high or repeated doses of exogenous opioids may lead to opioid intoxication and death (5.4)

### ADVERSE REACTIONS

Most common adverse reactions (incidence at least 2%) are nasal discomfort, headache, nausea, dizziness, hot flush, vomiting, anxiety, fatigue, nasal congestion, throat irritation, rhinalgia, decreased appetite, dysgeusia, erythema, and hyperhidrosis. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Indivior Inc. at 1-877-782-6966 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

OPVEE nasal spray is indicated for the emergency treatment of known or suspected overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression.

OPVEE nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present.

OPVEE nasal spray is not a substitute for emergency medical care.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Administration Instructions

- OPVEE is for intranasal use only.
- The device is ready to use. No device assembly is required.
- Do not prime or test prior to administration. OPVEE nasal spray delivers its entire contents automatically, upon activation.
- Do not attempt to reuse OPVEE. Each unit-dose device contains a single dose of nalmeferene and cannot be reused.
- No device assembly is required.
- Because treatment of suspected opioid overdose must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about the presence of OPVEE nasal spray and the *Instructions for Use*.
- Instruct the patient or caregiver to read the *Instructions for Use* at the time they receive a prescription for OPVEE nasal spray. Emphasize the following instructions to the patient or caregiver:
  - Administer OPVEE nasal spray as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death.
  - Always seek emergency medical assistance after administration of the first dose of OPVEE nasal spray in the event of a suspected, potentially life-threatening opioid emergency. Keep the patient under continued surveillance until emergency personnel arrive.
  - Additional doses of OPVEE nasal spray may be required until emergency medical assistance becomes available.
  - Re-administer OPVEE nasal spray, using a new nasal spray, in the nose, every 2 to 5 minutes if the patient does not respond or responds and then relapses into respiratory depression.
  - Administer OPVEE nasal spray according to the printed instructions on the *Quick Start Guide* and the *Instructions for Use*.
    - Place the patient in the supine position. Prior to administration, be sure the device nozzle is inserted in the nose of the patient and provide support to the back of the neck to allow the head to tilt back. Do not prime or test the device prior to administration.
    - To administer the dose, press firmly on the device plunger and remove the device nozzle from the nose after use.
    - If the patient responds by waking up to the voice or touch or starts breathing normally, place the patient on their side (recovery position) as shown in the *Instructions for Use* and call for emergency medical assistance immediately after administration of the first dose of OPVEE nasal spray.

## **2.2 Dosing in Adults and Pediatric Patients aged 12 years and older**

### Initial Dosing:

The recommended initial dose of OPVEE nasal spray in adults and pediatric patients aged 12 years and older is one spray delivered by intranasal administration, which delivers 2.7 mg of nalmefene.

### Repeat Dosing:

Seek emergency medical assistance as soon as possible after intranasal administration of the first dose of OPVEE nasal spray. The requirement for repeat doses of OPVEE nasal spray (2.7 mg) depends upon the amount, type, and route of administration of the opioid being antagonized.

If the patient responds to OPVEE nasal spray and relapses back into respiratory depression before emergency assistance arrives, administer an additional dose of OPVEE in the opposite nostril using a new OPVEE nasal spray and continue surveillance of the patient.

If the desired response is not obtained after 2 to 5 minutes, administer an additional dose of OPVEE using a new OPVEE nasal spray device. If there is still no response and additional doses are available, administer additional doses of OPVEE nasal spray every 2 to 5 minutes using a new OPVEE nasal spray device with each dose until emergency medical assistance arrives.

Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

## **2.3 Dosing Modifications due to Partial Agonists or Mixed Agonists/Antagonists**

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and require repeated administration of OPVEE nasal spray using a new nasal spray device [*see Warnings and Precautions (5.2)*].

## **3 DOSAGE FORMS AND STRENGTHS**

Nasal spray: 2.7 mg nalmefene per device. Each unit-dose nasal spray device delivers a single spray containing 2.7 mg of nalmefene.

## **4 CONTRAINDICATIONS**

OPVEE nasal spray is contraindicated in patients known to be hypersensitive to nalmefene or to any of the other ingredients.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Risk of Recurrent Respiratory and Central Nervous System Depression**

Respiratory depression in the community overdose setting may be complex and involve

the effects of multiple or unknown drugs, some of which may be long-acting opioids. While the duration of action of nalmefene is as long as most opioids, a recurrence of respiratory depression is possible, even after an apparently adequate initial response to OPVEE nasal spray treatment [See *Clinical Pharmacology, Pharmacodynamics (12.3)*]. Therefore, it is necessary to seek emergency medical assistance immediately after administration of the first dose of OPVEE nasal spray and to keep the patient under continued surveillance. A second dose may be necessary if there is recurrence of symptoms of opioid overdose. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance [see *Dosage and Administration (2.2)*].

## **5.2 Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists**

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete. Repeat doses of OPVEE nasal spray may be required to antagonize buprenorphine because the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor [see *Dosage and Administration (2.3)*]. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

## **5.3 Precipitation of Severe Opioid Withdrawal**

The use of OPVEE in patients who are opioid dependent may precipitate opioid withdrawal characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure.

Abrupt postoperative reversal of opioid depression after using OPVEE may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. After use of OPVEE, monitor patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary edema associated with the use of nalmefene is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

OPVEE is not indicated for use in patients less than 12 years of age. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes. Monitor the patient for the development of the signs and symptoms of opioid withdrawal. There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. In these settings, use an alternative, opioid antagonist product that can be

titrated to effect and, where applicable, dosed according to weight. [see *Use in Specific Populations (8.4)*].

#### 5.4 Risk of Opioid Overdose from Attempts to Overcome the Blockade

OPVEE is unlikely to produce acute withdrawal symptoms in non-opioid dependent patients. The use of OPVEE nasal spray in patients who are opioid dependent may precipitate opioid withdrawal. Attempting to overcome opioid withdrawal symptoms caused by opioid antagonists with high or repeated doses of exogenous opioids could lead to opioid intoxication and death. Inform patients of the potential consequences of trying to overcome the opioid blockade. Get emergency medical assistance as soon as possible after use of OPVEE nasal spray regardless of withdrawal symptoms.

### 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Recurrent Respiratory and Central Nervous System Depression [see *Warnings and Precautions (5.1)*]
- Precipitation of Severe Opioid Withdrawal [see *Warnings and Precautions (5.3)*]

#### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OPVEE nasal spray is supported by safety and pharmacokinetic studies of OPVEE nasal spray in healthy subjects in a normal state and under steady state opioid agonism. The following adverse reactions were observed.

In a pharmacokinetic study of 66 healthy adult volunteers exposed to one spray of OPVEE nasal spray in one nostril the most common adverse reactions were: nasal discomfort and dizziness.

In a second pharmacokinetic study of 24 healthy adult volunteers exposed to one spray of OPVEE nasal spray in one nostril, two sprays of OPVEE nasal spray in one nostril or one spray of OPVEE nasal spray in each nostril, the most common adverse reactions were: rhinalgia, nasal congestion, nasal discomfort and nausea.

In a pharmacodynamic study of 61 healthy adult volunteers exposed to one spray of OPVEE nasal spray in one nostril, the most common adverse reactions were: headache, nausea, hot flush and dizziness.

**Table 1: Relative Frequencies of Treatment-Related Common Adverse Events That Occurred in Greater Than 1% of Healthy Adult Volunteers**

	Nalmefene 2.7 mg		Nalmefene 5.4 mg		
	Total 2.7 mg	PD Study	PK Studies	PK Study (1 spray in each nostril)	PK Study (2 sprays in one nostril)

<b>System Organ Class Preferred Term</b>	<b>N=150 n (%)</b>	<b>N=61 n (%)</b>	<b>N=89 n (%)</b>	<b>N=23 n (%)</b>	<b>N=24 n (%)</b>
<b>Respiratory, thoracic and mediastinal disorders</b>					
Nasal discomfort	43 (28.7%)	5 (8.2%)	38 (42.7%)	3 (13.0%)	3 (12.5%)
Nasal congestion	6 (4.0%)	2 (3.3%)	4 (4.5%)	1 (4.3%)	4 (16.7%)
Throat irritation	6 (4.0%)	3 (4.9%)	3 (3.4%)	0	0
Rhinalgia	4 (2.7%)	1 (1.6%)	3 (3.4%)	2 (8.7%)	6 (25.0%)
Dyspnea	2 (1.3%)	2 (3.3%)	0	0	0
Oropharyngeal pain	2 (1.3%)	2 (3.3%)	0	1 (4.3%)	1 (4.2%)
<b>Nervous system disorders</b>					
Headache	40 (26.7%)	34 (55.7%)	6 (6.7%)	1 (4.3%)	0
Dizziness	14 (9.3%)	9 (14.8%)	5 (5.6%)	0	1 (4.2%)
Dysgeusia	3 (2.0%)	2 (3.3%)	1 (1.1%)	0	0
Paresthesia	2 (1.3%)	2 (3.3%)	0	1 (4.3%)	1 (4.2%)
Presyncope	0	0	0	1 (4.3%)	0
<b>Gastrointestinal disorders</b>					
Nausea	25 (16.7%)	22 (36.1%)	3 (3.4%)	5 (21.7%)	1 (4.2%)
Vomiting	9 (6.0%)	7 (11.5%)	2 (2.2%)	1 (4.3%)	0
Abdominal pain	2 (1.3%)	1 (1.6%)	1 (1.1%)	0	0
Dry mouth	1 (0.7%)	1 (1.6%)	0	1 (4.3%)	0
Constipation	0	0	0	0	1 (4.2%)
<b>Vascular disorders</b>					
Hot flush	12 (8.0%)	12 (19.7%)	0	0	0
<b>Psychiatric disorders</b>					
Anxiety	7 (4.7%)	7 (11.5%)	0	0	0
Agitation	2 (1.3%)	2 (3.3%)	0	0	0
Claustrophobia	2 (1.3%)	2 (3.3%)	0	0	0
Insomnia	1 (0.7%)	0	1 (1.1%)	1 (4.3%)	0
<b>General disorders and administration site conditions</b>					
Fatigue	6 (4.0%)	3 (4.9%)	3 (3.4%)	0	0
Chills	2 (1.3%)	2 (3.3%)	0	0	0
Chest discomfort	0	0	0	1 (4.3%)	0
<b>Skin and subcutaneous tissue disorders</b>					
Erythema	3 (2.0%)	0	3 (3.4%)	1 (4.3%)	1 (4.2%)
Hyperhidrosis	3 (2.0%)	3 (6.6%)	0	0	1 (4.2%)
Urticaria	0	0	0	0	1 (4.2%)
<b>Metabolism and nutrition disorders</b>					
Decreased appetite	3 (2.0%)	2 (3.3%)	1 (1.1%)	0	0
<b>Infections and infestations</b>					
Rhinitis	1 (0.7%)	0	1 (1.1%)	1 (4.3%)	0
<b>Eye disorders</b>					
Dry eye	0	0	0	1 (4.3%)	0

<b>Cardiac disorders</b>					
Tachycardia	0	0	0	1 (4.3%)	0

PK Studies OPNT003-PK-001 + OPNT003-PK-002 and PD Study OPNT003-  
OOD-001

Adverse reaction information was obtained following administration of nalmefene injection to 152 normal volunteers and in controlled clinical trials to 1127 patients for the treatment of opioid overdose or for postoperative opioid reversal.

**Table 2. Relative Frequencies of Common Adverse Reactions with an Incidence Greater than 1% (all patients, all clinical settings)**

Adverse Reaction	Nalmefene	Placebo
	N=1127	N=77
Nausea	18%	6%
Vomiting	9%	4%
Tachycardia	5%	-
Hypertension	5%	-
Postoperative Pain	4%	N/A
Fever	3%	-
Dizziness	3%	1%
Headache	1%	4%
Chills	1%	-
Hypotension	1%	-
Vasodilatation	1%	-

### **Incidence less than 1%**

Cardiovascular: Bradycardia, arrhythmia

Digestive: Diarrhea, dry mouth

Nervous System: Somnolence, depression, agitation, nervousness, tremor, confusion, withdrawal syndrome, myoclonus

Respiratory: Pharyngitis

Skin: Pruritus

Urogenital: Urinary retention

The incidence of adverse events was highest in patients who received more than the recommended dose of nalmefene injection.

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of nalmefene. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abrupt reversal of opioid depression using nalmefene in both postoperative and emergency department settings has resulted in nausea, vomiting, sweating, tremulousness, seizures, and cardiovascular instability including tachycardia,



hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects.

In persons who were physically dependent on opioids, abrupt reversal of opioid effects has precipitated an acute withdrawal syndrome. Signs and symptoms have included: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shiver or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In some patients, there may be aggressive behavior upon abrupt reversal of an opioid overdose. In the neonate, opioid withdrawal symptoms also included convulsions, excessive crying, and hyperactive reflexes.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Life-sustaining therapy for opioid overdose should not be withheld (*see Clinical Considerations*). There are no available data on nalmefene use in pregnant women to evaluate for a drug-associated risk of major birth defects or miscarriage. In animal reproduction studies, no embryotoxic effects on embryo-fetal development were observed in rats and rabbits treated with nalmefene at exposures at least 6 times (rats) and up to 20 times (rabbits) the exposure at two human nasal doses of 5.4 mg (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Clinical Considerations

##### *Disease-associated maternal and/or embryo/fetal risk*

An opioid overdose is a medical emergency and can be fatal for the pregnant woman and fetus if left untreated. Treatment with OPVEE for opioid overdose should not be withheld because of potential concerns regarding the effects of OPVEE on the fetus.

#### Data

##### *Animal Data*

Reproduction studies have been performed in rats (up to 1200 mg/m<sup>2</sup>/day) and rabbits (up to 2400 mg/m<sup>2</sup>/day) by oral administration of nalmefene and in rabbits by intravenous administration up to 96 mg/m<sup>2</sup>/day. No effects on embryo-fetal development were observed at exposures at least 6 times (rats) and up to 20 times (rabbits) the exposure corresponding to a human dose of 5.4 mg (two nalmefene nasal sprays) on an AUC basis. The treatment in rats did not affect offspring survival.

## **8.2 Lactation**

### Risk Summary

There are no data on the presence of nalmefene and its metabolites in human milk, the effects of nalmefene on the breastfed child, or the effects on milk production. Nalmefene and its metabolites are present in rat milk (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk.

### Data

Nalmefene and its metabolites were secreted into rat milk, reaching concentrations approximately three times those in plasma at one hour and decreasing to about half the corresponding plasma concentrations by 24 hours following bolus administration. The concentration of nalmefene in animal milk does not necessarily predict the concentration of drug in human milk.

## **8.4 Pediatric Use**

The safety and effectiveness of OPVEE nasal spray for the emergency treatment of known or suspected opioid overdose in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression, have been established.

Use for this indication in this age group is supported by adult studies and pharmacokinetic simulation [*see Clinical Pharmacology (12.3)*]. There have been no studies conducted to evaluate the use of OPVEE nasal spray in pediatric patients.

The safety and effectiveness of OPVEE nasal spray for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression have not been established in pediatric patients younger than 12 years of age.

## **8.5 Geriatric Use**

Clinical studies of OPVEE nasal spray did not include subjects aged 65 and over. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Geriatric patients have a greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Therefore, the systemic exposure of nalmefene can be higher in these patients.

## **8.6 Hepatic Impairment**

Hepatic impairment substantially reduces the clearance of nalmefene [*see Clinical Pharmacology (12.3)*]. For single episodes of opioid antagonism, adjustment of OPVEE nasal spray dosage is not required.

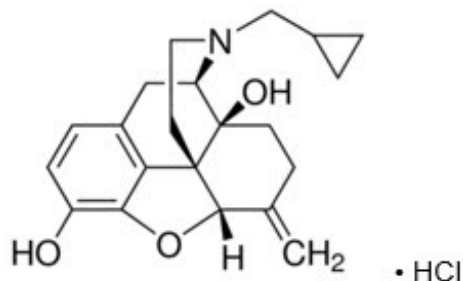
## **8.7 Renal Impairment**

Renal impairment substantially reduces the clearance of nalmefene [*see Clinical Pharmacology (12.3)*]. For single episodes of opioid antagonisms, adjustment of OPVEE nasal spray dosage is not required.

## **11 DESCRIPTION**

OPVEE (nalmeferne) nasal spray is a pre-filled, unit-dose intranasal spray.

Nalmeferne, an opioid antagonist, is a 6-methylene analogue of naltrexone. The molecular structure of nalmeferne is presented below:



Molecular Formula:  $C_{21}H_{25}NO_3 \cdot HCl$

Molecular Weight: 375.9, CAS # 58895-64-0

Chemical Name: 17-(Cyclopropylmethyl)-4,5 $\alpha$ -epoxy-6-methylenemorphinan-3,14-diol, hydrochloride salt.

Nalmeferne is a white to off-white crystalline powder which is freely soluble in methanol and water, with a pK of 7.63.

Each OPVEE nasal spray unit delivers 2.7 mg nalmeferne (equivalent to 3mg nalmeferne hydrochloride) in 0.1 mL solution.

Inactive ingredients include benzalkonium chloride, disodium ethylenediaminetetraacetate, dodecylmaltoside, sodium chloride, and purified water. The pH range is 4.1 to 4.9.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

OPVEE is an antagonist at opioid receptors.

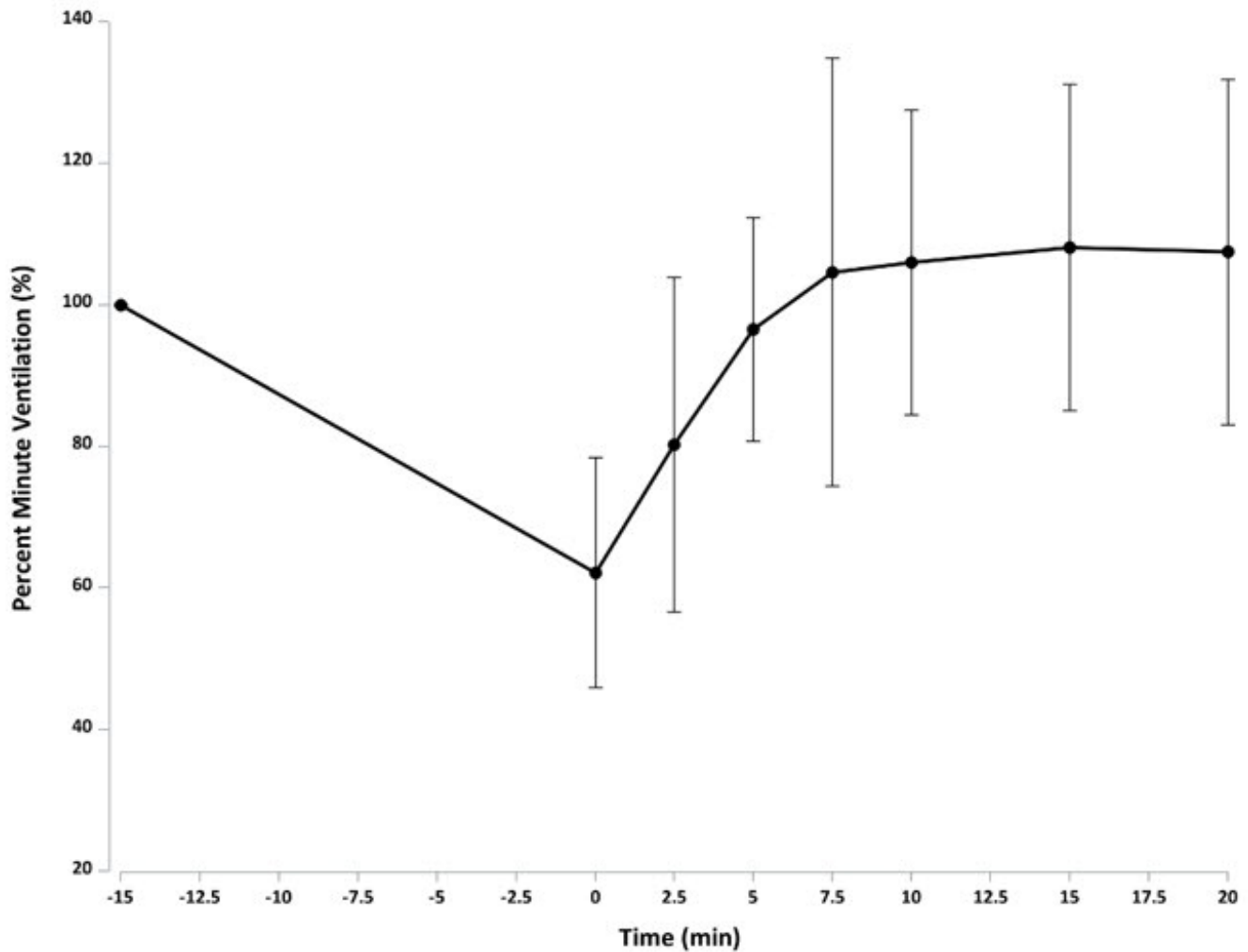
### 12.2 Pharmacodynamics

Nalmeferne reverses the effects of natural and synthetic opioids, including respiratory depression, sedation, and hypotension. Pharmacodynamic studies have shown that nalmeferne injection has a longer duration of action than naloxone injection at fully reversing doses. Nalmeferne has no opioid agonist activity.

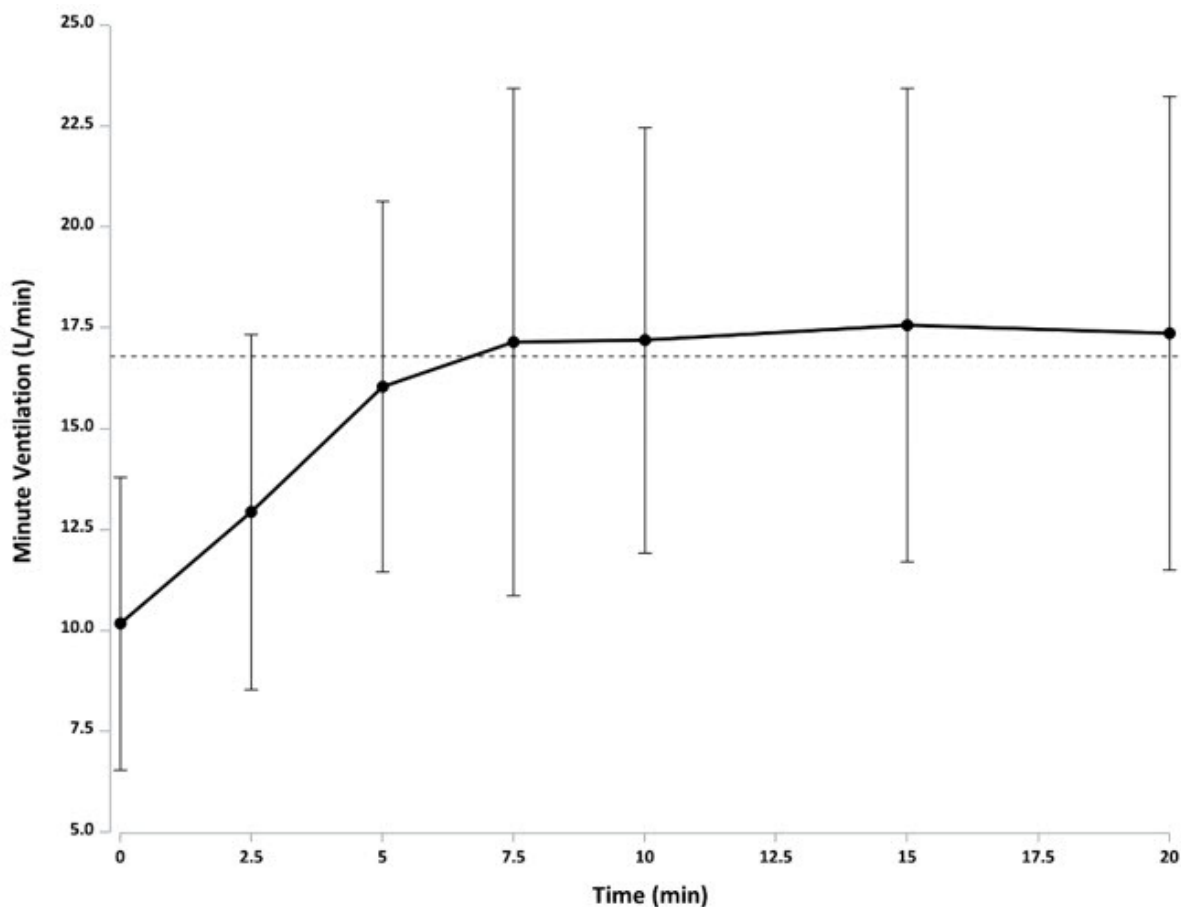
The effect of 2.7 mg OPVEE on remifentanil-induced respiratory depression in an experimental ventilatory-response to hypercapnia model, assessed by changes in minute ventilation (MV), was evaluated in sixty-one opioid-experienced, non-dependent subjects. In this study subjects started receiving a hypercapnic gas mixture (50% O<sub>2</sub>, 43% N<sub>2</sub>, 7% CO<sub>2</sub>) at -25 minutes. Just prior to initiation of remifentanil infusion at -15 minutes is the baseline MV (marked as 100% in Figure 1 and marked as observed data as liters/minute in Figure 2). Fifteen minutes after initiating remifentanil infusion, nadir in minute ventilation is observed at time zero, at which point OPVEE was administered. The

subjects were then monitored for changes in MV over 120 minutes. Following OPVEE administration the time to onset of effect, that is onset of reversal of respiratory depression, was observed between 2.5 to 5 minutes (Figure 1 and Figure 2). At 5 minutes the estimated mean increase in minute ventilation was 5.745 L/min (Figure 2). Full recovery of respiratory drive was noted between 5 and 15 minutes after OPVEE administration (Figure 1 and Figure 2).

**Figure 1: Percentage recovery of respiratory drive after infusion of remifentanyl in CO<sub>2</sub> stimulated minute ventilation (mean +/- standard deviation) in adult healthy volunteers treated with OPVEE (nalmeferne) nasal spray**



**Figure 2: Reversal of Remifentanyl-Induced Respiratory Depression (Mean Minute Ventilation +/- Standard Deviation) by OPVEE (nalmeferne) nasal spray**



Remifentanyl (an initial bolus of 0.5  $\mu\text{g}/\text{kg}$  dose followed by an infusion rate of 0.175  $\mu\text{g}/\text{kg}/\text{min}$ ) was administered for 15 min prior to test agents and continued for the duration of the study. The dashed line represents the mean minute ventilation (MV) prior to remifentanyl administration.

Based on population pharmacokinetic/pharmacodynamic model simulations, the EC<sub>50</sub> (drug concentration at which pharmacological effect is half maximum change in response) was 1.50 ng/mL for OPVEE following a single 2.7 mg administration. The time to reach EC<sub>50</sub> was 4 minutes for OPVEE. The plasma concentrations remained above the EC<sub>50</sub> for 5.94 hours for OPVEE.

Nalmefene is not known to produce respiratory depression, psychotomimetic effects, or pupillary constriction. No pharmacological activity was observed when nalmefene was administered in the absence of opioid agonists.

Nalmefene has not been shown to produce tolerance, physical dependence, or abuse potential.

Nalmefene can produce acute withdrawal symptoms in individuals who are opioid dependent.

### 12.3 Pharmacokinetics

In a pharmacokinetic study (OPNT003-PK-001) in 68 healthy adult subjects, the relative bioavailability of one 2.7 mg OPVEE nasal spray in one nostril (0.1 mL of 27 mg/mL nalmefene), was compared to a single dose of nalmefene 1.0 mg administered as an intramuscular injection. Subjects remained fully supine and were instructed to hold their breath during the intranasal spray administration. The pharmacokinetic parameters

obtained in this study are shown in Table 3 and the plasma concentration time profiles of nalmefene are presented in Figure 3.

**Table 3: Geometric Mean (CV%) PK Parameters of Nalmefene after Intranasal (IN) Administration of 2.7 mg OPVEE nasal spray and Intramuscular (IM) Administration of 1.0 mg of Nalmefene**

<b>Parameter</b>	<b>OPVEE</b>	<b>Nalmefene IM</b>
$T_{max}$ (h)*	0.250 (0.0833-2.00)	0.33 (0.117-18.0)
$C_{max}$ (ng/mL)†	10.4 (62.6)	1.50 (59.4)
$AUC_{0-2.5min}$ (ng-hr/mL)†	0.00763 (233)	0.00168 (186)
$AUC_{0-5min}$ (ng-hr/mL)†	0.0599 (201)	0.0102 (142)
$AUC_{0-10min}$ (ng-hr/mL)†	0.523 (124)	0.0639 (118)
$AUC_{0-15min}$ (ng-hr/mL)†	1.20 (94.2)	0.142 (98.6)
$AUC_{0-20min}$ (ng-hr/mL)†	1.89 (77.2)	0.228 (84.5)
$AUC_{0-30min}$ (ng-hr/mL)†	3.07 (60.4)	0.405 (69.2)
$AUC_{0-inf}$ (ng-hr/mL)†	40.6 (22.0)	16.8 (18.7)
$F_{rel}$ †	0.806 (10.9)	NA
$T_{1/2}$ (h)†	11.4 (20.8)	10.6 (18.5)

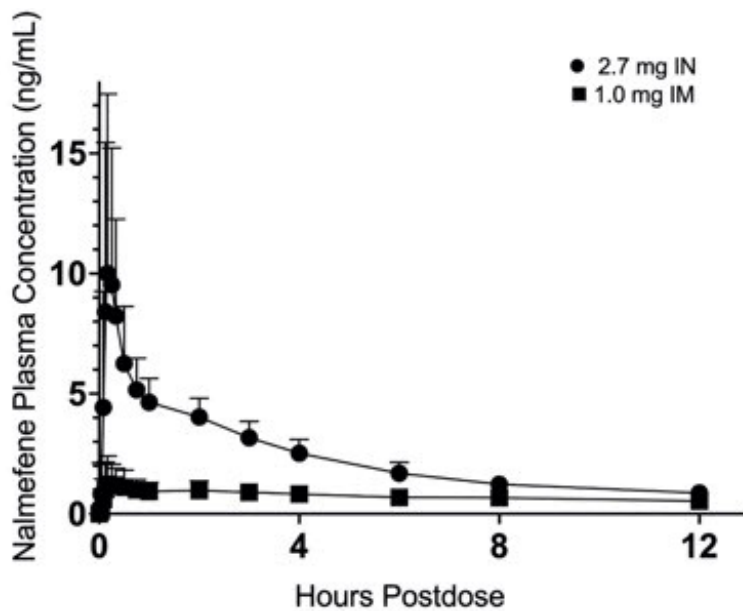
NA Not applicable

\*  $T_{max}$  presented as median (range)

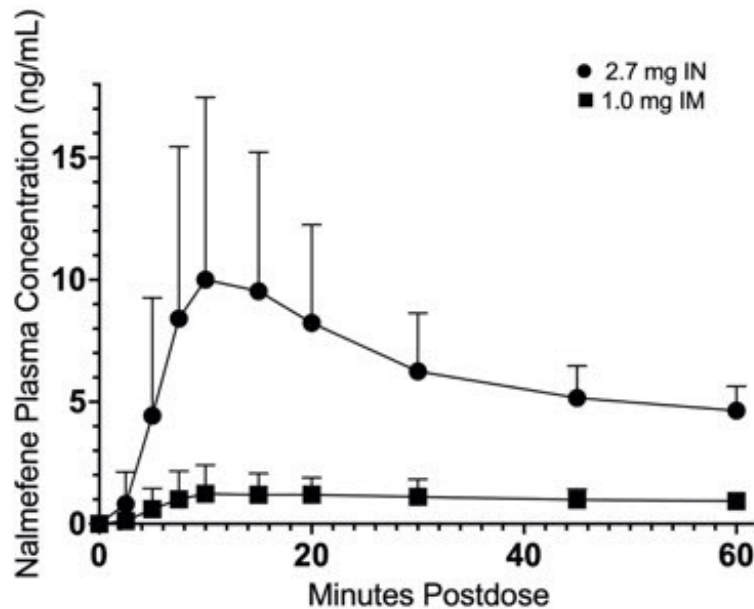
† Arithmetic mean

**Figure 3: Mean Plasma Concentration-Time Profiles of Nalmefene (a) 0-12 hours and (b) 0-60 minutes Following Intranasal (IN) Administration of OPVEE nasal spray (2.7 mg) and Intramuscular (IM) Injection of Nalmefene (1.0 mg)**

(a)



(b)



Values represent the mean and standard deviation (n=68)

In a second pharmacokinetic study (OPNT003-PK-002) in 24 healthy adult subjects, one 2.7 mg OPVEE nasal spray in one nostril was compared with two 2.7 mg OPVEE nasal sprays in one nostril and one 2.7 mg OPVEE nasal spray in each nostril. Subjects remained fully supine and were instructed to hold their breath during the intranasal spray administration. The pharmacokinetic parameters obtained in this study are shown in Table 4 and the plasma concentration time profiles of nalmefene are presented in Figure 4.

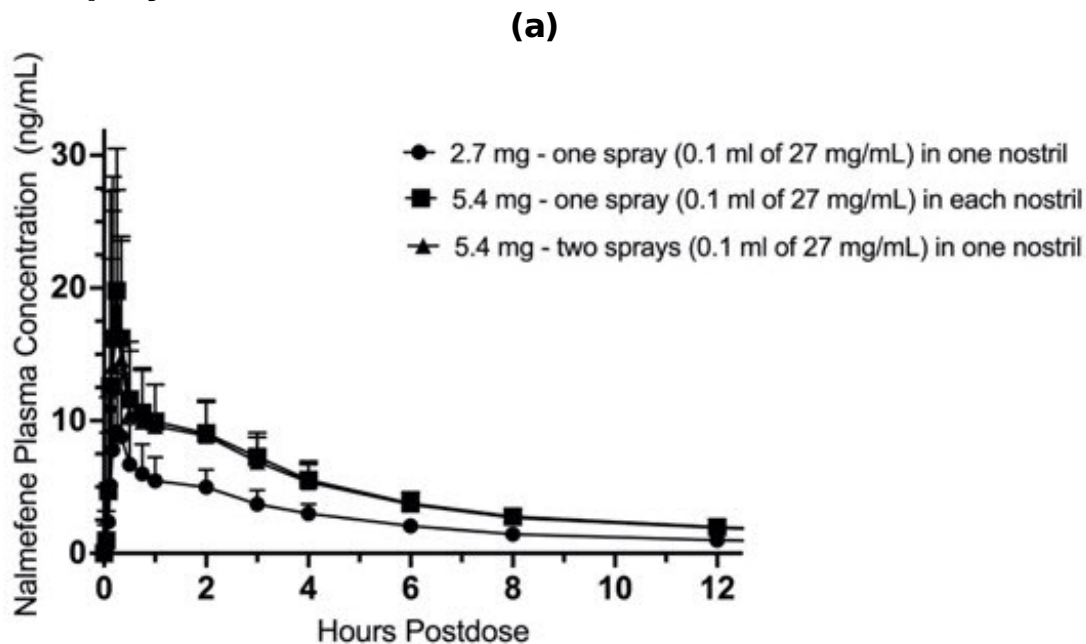
**Table 4: Geometric Mean (CV%) PK Parameters of Nalmefene After Intranasal (IN) Dose of 2.7 mg Nalmefene (One OPVEE nasal spray in One Nostril), IN Dose of 5.4 mg Nalmefene (One OPVEE nasal spray in Each Nostril) and IN Dose of 5.4 mg Nalmefene (Two OPVEE nasal sprays in One Nostril)**

Parameter	OPVEE 2.7mg (one spray)	OPVEE 5.4mg (one spray in each nostril)	OPVEE 5.4mg (two sprays in one nostril)
T <sub>max</sub> (h)*	0.267 (0.167- 2.03)	0.250 (0.117- 3.00)	0.250 (0.117- 2.03)
C <sub>max</sub> (ng/mL)	9.75 (49.4)	18.9 (88.0)	16.1 (62.9)
AUC <sub>0-2.5min</sub> (ng- hr/mL)	0.00594 (134)	0.0163 (217)	0.0172 (117)
AUC <sub>0-5min</sub> (ng- hr/mL)	0.0446 (99.6)	0.110 (161)	0.108 (92.9)
AUC <sub>0-10min</sub> (ng- hr/mL)	0.388 (72.1)	0.828 (102)	0.717 (93.2)
AUC <sub>0-15min</sub> (ng- hr/mL)	0.999 (65.9)	2.08 (81.8)	1.73 (83.0)
AUC <sub>0-20min</sub> (ng- hr/mL)	1.66 (61.3)	3.42 (69.9)	2.85(74.3)
AUC <sub>0-30min</sub> (ng- hr/mL)	2.83 (56.0)	5.63 (57.7)	4.78 (60.8)
AUC <sub>0-inf</sub> (ng- hr/mL)	45.8 (21.7)	88.1 (18.3)	83.8 (22.0)
T <sub>1/2</sub> (h)†	11.4 (22.0)	11.3 (16.6)	11.3 (16.5)

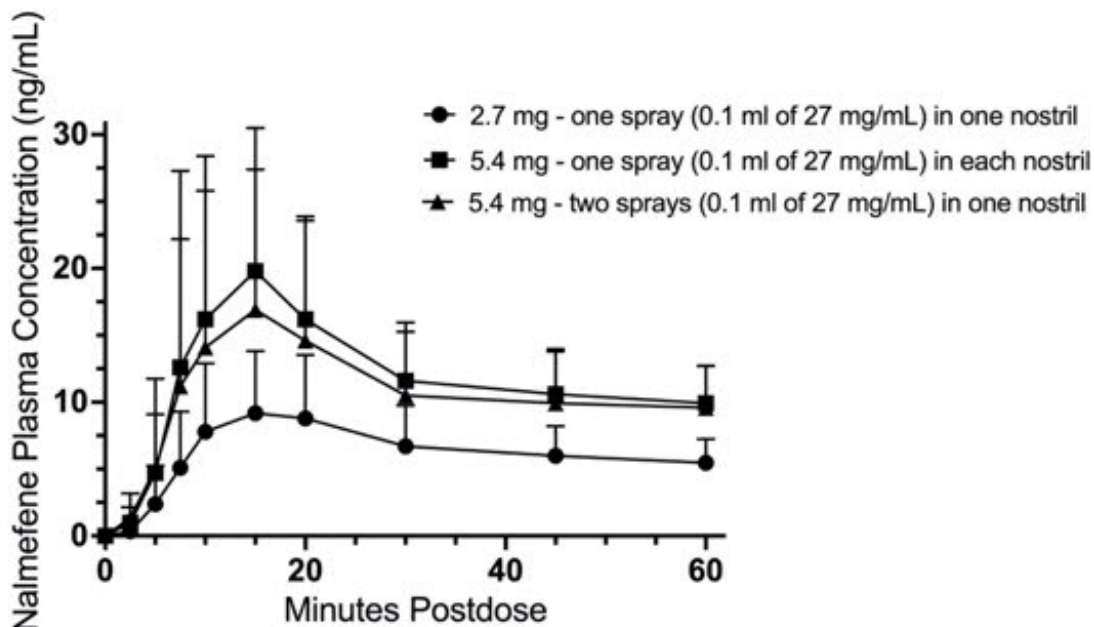
\* T<sub>max</sub> presented as median (range)

† Arithmetic mean

**Figure 4: Mean Plasma Concentration of Nalmefene, (a) 0-12 hours and (b) 0-60 minutes Following Intranasal (IN) Administration of 2.7 mg Nalmefene (One OPVEE nasal spray in One Nostril), IN Dose of 5.4 mg Nalmefene (One OPVEE nasal spray in Each Nostril) and IN Dose of 5.4 mg Nalmefene (Two OPVEE nasal sprays in One Nostril)**







Values represent the mean and standard deviation (n=24)

### Absorption

After administration of one 2.7 mg OPVEE nasal spray to healthy adult subjects, the median  $T_{max}$  for OPVEE was 0.250 hours, compared to 0.33 hours for the intramuscular nalmefene.

After administration of two 2.7 mg OPVEE nasal sprays (total dose 5.4mg) to healthy adult subjects, the median  $T_{max}$  for OPVEE was 0.250 hours.

The dose normalized area under the curve ( $AUC_{0-inf}$ ) to infinity is similar for one 2.7 mg OPVEE nasal spray in one nostril and one 2.7 mg OPVEE nasal spray in each nostril with a geometric mean ratio of 96.23% (90%CI 92.00%-100.65%). The dose normalized  $AUC_{0-inf}$  is also similar for one 2.7 mg OPVEE nasal spray in one nostril and two 2.7 mg OPVEE nasal sprays in one nostril with a geometric mean ratio of 91.19% (90%CI 87.19%-95.38%).

The mean bioavailability ( $F_{rel}$ ) of OPVEE was 0.806 relative to intramuscular administration of nalmefene.

### Distribution

Following a 1 mg parenteral dose, nalmefene was rapidly distributed. In a study of brain receptor occupancy, a 1 mg dose of nalmefene blocked over 80% of brain opioid receptors within 5 minutes after administration. The apparent volumes of distribution centrally ( $V_d$ ) and at steady-state ( $V_{ss}$ ) are  $3.9 \pm 1.1$  L/kg and  $8.6 \pm 1.7$  L/kg, respectively. Ultrafiltration studies of nalmefene have demonstrated that 45% (CV 4.1%) is bound to plasma proteins over a concentration range of 0.1 to  $2\mu\text{g/mL}$ . An in vitro determination of the distribution of nalmefene in human blood demonstrated that nalmefene distributed 67% (CV 8.7%) into red blood cells and 39% (CV 6.4%) into plasma. The whole blood to plasma ratio was 1.3 (CV 6.6%) over the nominal concentration range in whole blood from 0.376 to 30 ng/mL.

### Elimination

After administration of 2.7 mg OPVEE nasal spray to healthy adult subjects, plasma concentrations have a terminal elimination half-life of 11.4 (%CV 20.8) hours. The apparent clearance of nalmefene is 75.7 (%CV 23.8) L/hr.

### *Metabolism*

Nalmefene is metabolized by the liver, primarily by glucuronide conjugation.

Nalmefene is also metabolized to trace amounts of an N-dealkylated metabolite. Nalmefene glucuronide is inactive and the N-dealkylated metabolite has minimal pharmacological activity.

### *Excretion*

Nalmefene and its metabolites are excreted in the urine. Less than 5% of nalmefene is excreted in the urine unchanged. Seventeen percent (17%) of the nalmefene dose is excreted in the feces. The plasma concentration-time profile in some subjects suggests that nalmefene undergoes enterohepatic recycling.

### Specific Populations

#### *Geriatric Patients*

In previous studies with nalmefene hydrochloride injection, dose proportionality was observed in nalmefene AUC following 0.5 to 2 mg intravenous administration to elderly male subjects. Following a 1 mg intravenous nalmefene dose, there were no significant differences between young (19-32 years) and elderly (62-80 years) adult male subjects with respect to plasma clearance, steady-state volume of distribution, or half-life. There was an apparent age-related decrease in the central volume of distribution (young:  $3.9 \pm 1.1$  L/kg, elderly:  $2.8 \pm 1.1$  L/kg) that resulted in a greater initial nalmefene concentration in the elderly group. While initial nalmefene plasma concentrations were transiently higher in the elderly, it would not be anticipated that this population would require dosing adjustment. No clinical adverse events were noted in the elderly following the 1 mg intravenous nalmefene dose.

#### *Pediatric Patients*

No pharmacokinetic studies were conducted with OPVEE nasal spray in pediatric patients. Based on population PK simulations, compared to an adult population (mean weight 75.42 kg), 12-year-old subjects with a median weight 50.6 kg, range 27.6 to 126.8 kg are expected to have 7.6% higher mean  $C_{max}$  and 25.5% higher mean  $AUC_{0-\infty}$  [See *Pediatric Use* (8.4)].

#### *Male and Female Patients*

There has not been sufficient pharmacokinetic study to make a definitive statement as to whether the pharmacokinetics of nalmefene differs between the male and female patients.

#### *Patients with Renal Impairment*

The pharmacokinetics of OPVEE nasal spray have not been studied in renally impaired subjects. In previous studies with nalmefene hydrochloride injection, there was a statistically significant 27% decrease in plasma clearance of nalmefene in the end-stage renal disease (ESRD) population during interdialysis ( $0.57 \pm 0.20$  L/hr/kg) and a 25% decreased plasma clearance in the ESRD population during intradialysis ( $0.59 \pm 0.18$  L/hr/kg) compared to healthy volunteers ( $0.79 \pm 0.24$  L/hr/kg). The elimination half-life

was prolonged in ESRD patients from  $10.2 \pm 2.2$  hours in healthy volunteers to  $26.1 \pm 9.9$  hours.

#### *Patients with Hepatic Impairment*

No pharmacokinetic studies were conducted with OPVEE nasal spray in hepatically impaired subjects. In previous studies with nalmefene hydrochloride injection, subjects with hepatic disease, when compared to matched normal controls, had a 28.3% decrease in plasma clearance of nalmefene ( $0.56 \pm 0.21$  L/hr/kg versus  $0.78 \pm 0.24$  L/hr/kg, respectively). Elimination half-life increased from  $10.2 \pm 2.2$  hours to  $11.9 \pm 2.0$  hours in the hepatically impaired. No dosage adjustment is recommended since OPVEE nasal spray will be administered as an acute course of therapy.

#### *Low Body Weight Patients and High Body Weight Patients*

The effect of weight on nalmefene PK following a single intranasal 2.7 mg OPVEE administration was assessed using population pharmacokinetic simulations. Compared to the mean PK values across the full population in the PK dataset (median weight 74.70 kg), the 1st quartile of body weight (50.4 to 64.8 kg) had + 5.2% higher  $C_{max}$  and + 15.7% higher  $AUC_{0-\infty}$  whereas the 4th quartile of body weight (91 to 106.8 kg) had - 4.4% lower  $C_{max}$  and - 11.6% lower  $AUC_{0-\infty}$ .

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

The carcinogenic potential of nalmefene has not been evaluated.

#### Mutagenesis

Nalmefene did not have mutagenic activity in the Ames test with five bacterial strains or the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test or in the cytogenic bone marrow assay in rats. However, nalmefene did exhibit a weak but significant clastogenic activity in the human lymphocyte metaphase assay in the absence but not in the presence of exogenous metabolic activation.

#### Impairment of Fertility

Oral administration of nalmefene up to 1200 mg/m<sup>2</sup>/day did not affect fertility in rats at exposures at least 6 times the exposure corresponding to a human dose of 5.4 mg (two nalmefene nasal sprays) on an AUC basis.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**

Each unit-dose nasal spray device delivers 2.7 mg of nalmefene (equivalent to 3 mg of nalmefene hydrochloride) in 0.1 mL. Each carton contains two unit-dose nasal spray devices.

NDC # 12496-0003-2

OPVEE is not made with natural rubber latex.

## **16.2 Storage and Handling**

Store OPVEE nasal spray in the blister and cartons provided.

Store OPVEE nasal spray at controlled room temperature 15°C to 25°C (59°F to 77°F). Short-term excursions permitted between 4°C to 40°C (39°F to 104°F). Do not freeze. Protect from light.

Do not open individual blister packs or test nasal spray devices before use.

Each unit-dose nasal spray device sprays one (1) time and cannot be re-used.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient and family members or caregivers to read the FDA-approved patient labeling (*Patient Information and Instructions for Use*).

### Recognition of Opioid Overdose

Inform patients and their family members or caregivers about how to recognize the signs and symptoms of an opioid overdose such as the following:

- Extreme somnolence -inability to awaken a patient verbally or upon a firm sternal rub.
- Respiratory depression -this can range from slow or shallow respiration to no respiration in a patient who is unarousable.
- Other signs and symptoms that may accompany somnolence and respiratory depression include the following:
  - Miosis
  - Bradycardia and/or hypotension.

### Risk of Recurrent Respiratory Depression

While the duration of action of nalmeferene is as long as most opioids, instruct patients and their family members or caregivers that they must seek immediate emergency medical assistance after administration of the first dose of OPVEE and keep the patient under continued surveillance, even after an apparently adequate initial response to OPVEE nasal spray treatment. A second dose may be necessary if there is recurrence of symptoms of opioid overdose [see *Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)*].

### Limited Efficacy for/with Partial Agonists or Mixed Agonist/Antagonists

Instruct patients and their family members or caregivers that the reversal of respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and may require repeated administration of OPVEE nasal spray, using a new nasal spray device each time [see *Dosage and Administration (2.3)*, *Warnings and Precautions (5.2)*].

### Precipitation of Severe Opioid Withdrawal

Instruct patients and their family members or caregivers that the use of OPVEE nasal spray in patients who are opioid dependent may precipitate opioid withdrawal [see *Warnings and Precautions (5.3)*, *Adverse Reactions (6)*].

## Administration Instructions

Instruct patients and their family members or caregivers to:

- Ensure OPVEE is readily available in locations where persons may be intentionally or accidentally exposed to an opioid overdose (i.e., opioid emergencies).
- Use each OPVEE device only one time. Do not test or prime prior to use [see *Dosage and Administration (2.1)*].
- Administer OPVEE as quickly as possible if a patient is unresponsive and an opioid overdose is suspected, even when in doubt, because prolonged respiratory depression may result in damage to the central nervous system or death. OPVEE is not a substitute for emergency medical care [see *Dosage and Administration (2.1)*].
- Lay the patient on their back and administer OPVEE into one nostril while providing support to the back of the neck to allow the head to tilt back [see *Dosage and Administration (2.1)*].
- Hold the OPVEE nasal spray device with your fingers on either side of the nozzle and thumb on the white plunger.
- Insert the nozzle into the nose.
- Press the plunger firmly to give a dose in the nose.
- The dose has been delivered when the white plunger has been pushed all the way down until it stops.
- Remove the OPVEE nasal spray from the nose after the dose has been given.
- Call 911 after giving the first dose of OPVEE nasal spray.
- Put the person on their side in the recovery position.
- Watch the person carefully. Wait 2 to 5 minutes to see if the person wakes up.
- If the patient responds by waking up to the voice or touch or starts breathing normally, place them in the recovery position by turning them to their side as shown in the Instructions for Use and call for emergency medical assistance immediately after administration of OPVEE. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance [see *Dosage and Administration (2.1)*].
- Monitor the patient and re-administer additional doses of OPVEE every 2 to 5 minutes, using a new OPVEE device. If the patient is not responding or responds and then relapses back into respiratory depression, administer OPVEE in alternate nostrils with each dose [see *Dosage and Administration (2.1)*].
- Remain with the person until emergency medical help arrives.
- Replace OPVEE before its expiration date.

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Manufactured for: Indivior Inc., North Chesterfield, VA, 23235, USA

### **PATIENT INFORMATION**

**OPVEE (op vee)  
(nalmefene)  
nasal spray**

You and your family members or caregivers should read this Patient Information leaflet before an opioid emergency happens. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is the most important information I should know about OPVEE nasal**

## spray?

OPVEE nasal spray is used to temporarily reverse the effects of opioid medicines. The medicine in OPVEE nasal spray is not expected to have an effect in people who are not taking opioid medicines. Always carry OPVEE nasal spray with you in case of an opioid emergency.

1. Use OPVEE nasal spray right away if you or your caregiver think signs or symptoms of an opioid emergency are present, even if you are not sure, because an opioid emergency can cause severe injury or death. Signs and symptoms of an opioid emergency may include:
  - unusual sleepiness and you are not able to awaken the person with a loud voice or rubbing firmly on the middle of their chest (sternum)
  - breathing problems including slow or shallow breathing in someone difficult to awaken or who looks like they are not breathing
  - the black circle in the center of the colored part of the eye (pupil) is very small, sometimes called "pinpoint pupils" in someone difficult to awaken
2. Family members, caregivers, or other people who may have to use OPVEE nasal spray in an opioid emergency should know where OPVEE nasal spray is stored and how to give it before an opioid emergency happens.
3. **Call 911 or get emergency medical help right away after giving the first dose of OPVEE nasal spray.** Rescue breathing or CPR (cardiopulmonary resuscitation) may be given while waiting for emergency medical help.
4. The signs and symptoms of an opioid emergency can return after OPVEE nasal spray is given. If this happens, give another dose every 2 to 5 minutes using a new OPVEE nasal spray and watch the person closely until emergency help is received.

## What is OPVEE nasal spray?

- OPVEE nasal spray is a prescription medicine used in adults and children 12 years of age and older for the treatment of an opioid emergency such as an overdose or a possible opioid overdose with signs of breathing problems and severe sleepiness or not being able to respond.
- OPVEE nasal spray is to be given right away and does not take the place of emergency medical care. Get emergency medical help right way after giving the first dose of OPVEE nasal spray, even if the person wakes up.

It is not known if OPVEE nasal spray is safe and effective in children younger than 12 years of age.

**Do not use OPVEE nasal spray if you** are allergic to nalmefene or any of the ingredients in OPVEE nasal spray. See the end of this leaflet for a complete list of ingredients in OPVEE nasal spray.

**Before using OPVEE nasal spray, tell your healthcare provider about all of your medical conditions, including if you:**

- have heart problems
- are pregnant or plan to become pregnant. Use of OPVEE nasal spray may cause withdrawal symptoms in your unborn baby. Your unborn baby should be examined by a healthcare provider right away after you use OPVEE nasal spray.
- are breastfeeding or plan to breastfeed. It is not known if OPVEE nasal spray passes into your breast milk.

**Tell your healthcare provider about the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements.

## How should I use OPVEE nasal spray?

Read the "Instructions for Use" at the end of this Patient Information leaflet for detailed information about how to use OPVEE nasal spray.

- Use OPVEE nasal spray exactly as prescribed by your healthcare provider.
- Each OPVEE nasal spray only contains 1 dose of medicine and cannot be reused.
- Do not test or prime OPVEE nasal spray before use.
- Lay the person on their back. Use your hand to support behind their neck and allow the head to tilt back before giving OPVEE nasal spray.
- OPVEE nasal spray should be given into one nostril.
- If additional doses are needed, give OPVEE nasal spray in the other nostril.

## What are the possible side effects of OPVEE nasal spray?

OPVEE nasal spray may cause serious side effects, including:

- **Sudden opioid withdrawal symptoms.** In someone who has been using opioids regularly, opioid withdrawal symptoms can happen suddenly after receiving OPVEE nasal spray and may include:
  - body aches
  - diarrhea
  - increased heart rate
  - fever
  - runny nose
  - sneezing
  - goose bumps
  - sweating
  - yawning
  - nausea or vomiting
  - nervousness
  - restlessness or irritability
  - shivering or trembling
  - stomach cramping
  - weakness
  - increased blood pressure
- **Risk of opioid overdose.** OPVEE nasal spray blocks the effects of opioids and may cause opioid withdrawal in someone who has been using opioids regularly. **Do not** take large amounts of opioids to try to overcome the opioid-blocking effects of OPVEE nasal spray. This could lead to an opioid overdose and death. Call 911 or get emergency medical help right away after using OPVEE nasal spray.

**The most common side effects of OPVEE nasal spray include:**

- nose (nasal) discomfort
- headache
- nausea
- dizziness
- hot flush
- vomiting
- anxiety
- tiredness
- nasal congestion
- throat irritation
- pain in the nose
- decreased appetite
- changes in the sense of taste
- skin redness
- increased sweating

These are not all of the possible side effects of OPVEE nasal spray.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

## How should I store OPVEE nasal spray?

- Store OPVEE nasal spray at room temperature between 59°F to 77°F (15°C to 25°C).
- Do not freeze OPVEE nasal spray.
- Keep OPVEE nasal spray in its box until ready to use.
- Protect from light.
- Replace OPVEE nasal spray before the expiration date on the box.

**Keep OPVEE nasal spray and all medicines out of the reach of children.**

**General information about the safe and effective use of OPVEE nasal spray.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use OPVEE nasal spray for a condition for which it was not prescribed. You can ask your pharmacist or healthcare provider for information about OPVEE nasal spray that is written for health professionals.

**What are the ingredients in OPVEE nasal spray?**

**Active ingredient:** nalmefene

**Inactive ingredients:** benzalkonium chloride, disodium ethylenediaminetetraacetate, dodecyl maltoside, sodium chloride, and purified water.

OPVEE nasal spray is not made with natural rubber latex.

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Manufactured for: Indivior Inc., North Chesterfield, VA, 23235, USA

For more information, visit [www.OPVEE.com](http://www.OPVEE.com) or call 1-877-782-6966

This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: 06/2023

**INSTRUCTIONS FOR USE**

**OPVEE (op vee)  
(nalmefene)  
nasal spray**

The Instructions for Use contains information on how to give OPVEE nasal spray in response to a known or suspected opioid overdose in adults and children 12 years of age and older. You and your family members or caregivers should read the Instructions for Use that comes with OPVEE nasal spray before using it. Talk to your healthcare provider if you and your family members or caregivers have any questions about the use of OPVEE nasal spray.



**Important Information You Need to Know Before Giving OPVEE nasal spray**

- **For use in the nose only.**
- **Do not remove or test the OPVEE nasal spray before use.**
- **Each OPVEE nasal spray has 1 dose and cannot be reused.**
- **You do not need to prime OPVEE nasal spray.**

**Check for response**

**Step 1. Shout** "wake up" and **shake** the person gently.

If there is no response, slow breathing, or no breathing, lay the person flat on their back (**Figure A**).



**Figure A**



### Prepare to give OPVEE nasal spray

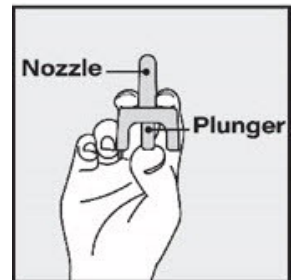
**Step 2.** Remove OPVEE nasal spray from the box. Peel off the back from the top corner to open the OPVEE nasal spray blister (**Figure B**).

**Step 3.** Hold the OPVEE nasal spray with your fingers on both sides of the nozzle and your thumb on the white plunger (**Figure C**).

**Do not press the plunger yet.**



**Figure B**



**Figure C**

### Give OPVEE nasal spray

**Step 4.** Provide support behind the neck with your hand and tilt the person's head back (**Figure D**).

**Step 5.** Gently insert the nozzle into one nostril until your fingers on either side of the nozzle are against the bottom of the person's nose. (**Figure D**).

**Step 6.** Press the plunger firmly to give the dose of OPVEE nasal spray in the nose.

The dose has been delivered when the white plunger has been pushed all the way down until it stops.

**Step 7.** Remove the OPVEE nasal spray from the nostril after the dose has been given.



**Figure D**

### After giving OPVEE nasal spray

**Step 8.** Call 911 or get emergency medical help right away (**Figure E**).

**Step 9.** Move the person on their side (recovery position) (**Figure F**):

- Hand is supporting their head.
- Bend their knee.
- Turn their face to the side.

**Step 10.** Wait for 2 to 5 minutes to see if the person wakes up. If the person does not respond by waking up, to voice or touch, or start breathing normally, another dose may be given (**Figure G**).

- Get a new OPVEE nasal spray from the box.
- Repeat Steps 1 through 7 to give another dose of OPVEE in the other nostril.

- If more OPVEE nasal sprays are available, repeat Steps 1 through 7



**Figure E**

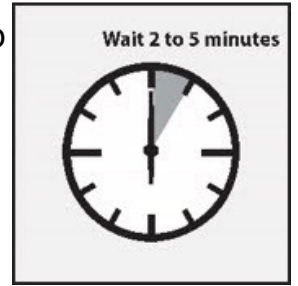


**Figure F**

- If more OPVEE nasal sprays are available, repeat steps 1 through 7 every 2 to 5 minutes, alternating nostrils, until the person wakes up or medical help arrives.

Stay with the person until medical help arrives.

**Step 11.** After OPVEE nasal spray has been used, put it back into its box. Throw away (dispose of) the used OPVEE nasal spray in a place that is away from children.



**Figure G**

### **Storing OPVEE nasal spray**

- Store OPVEE nasal spray at room temperature between 59°F to 77°F (15°C to 25°C).
- Do not freeze OPVEE nasal spray.
- Keep OPVEE nasal spray in its box until ready to use.
- Protect from light.
- Replace OPVEE nasal spray before the expiration date on the box.

**Keep OPVEE nasal spray and all medicines out of the reach of children.**

For more information about OPVEE nasal spray, go to [www.OPVEE.com](http://www.OPVEE.com) or call 1-877-782-6966.

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Issued: 06/2023

### **OPVEE®**

(nalmeffene)

**nasal spray**

### **QUICK START GUIDE**

**Use OPVEE nasal spray for known or suspected opioid overdose in adults and children 12 years of age and older.**

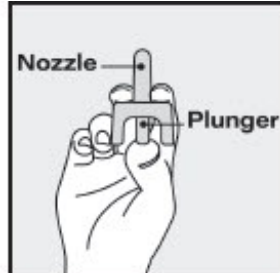
- **Important:** OPVEE nasal spray is for use **in the nose only**.
- **Do not remove or test** OPVEE nasal spray before use.
- Each OPVEE nasal spray has 1 dose and cannot be reused.
- You do not need to prime OPVEE nasal spray.

### **1. Check for response**



- **Shout** "wake up" and **shake** the person gently.
- If there is no response, slow breathing, or no breathing, **lay the person flat on their back**.

## 2. Prepare



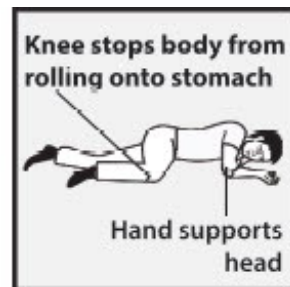
- **Remove** OPVEE nasal spray from the box.
- **Peel** off the back from the top corner to open the OPVEE nasal spray blister.
- **Hold** the OPVEE nasal spray with your fingers on both sides of the nozzle and your thumb on the white plunger.
- **Do not press the plunger yet.**

## 3. Give a dose in the nose



- Provide support behind the neck with your hand and tilt the person's head back.
- **Gently insert the nozzle into one nostril** until your fingers on either side of the nozzle are against the bottom of the person's nose.
- **Push the plunger firmly** all the way down until it stops to give a dose.

## 4. Call 911 and place person on their side



- **Call 911 or get emergency medical help right away.**
- **Move the person on their side (recovery position).**
- Stay with the person until medical help arrives.

## 5. Watch and give another dose



- **Wait 2 to 5 minutes** to see if the person wakes up.
- If the person does not wake up:
  - **Get a new OPVEE nasal spray** from the box.
  - **Give another dose** in the other nostril.
  - If more OPVEE nasal sprays are available, repeat Steps 1 through 3 every 2 to 5 minutes, alternating nostrils, until the person wakes up or medical help arrives.

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Manufactured for: Indivior  
Inc., North Chesterfield, VA,  
23235, USA

**PRINCIPAL DISPLAY PANEL - 2.7 mg Bottle Carton**

NDC 12496-0003-2

Rx only

OPVEE®  
(nalmefene)  
NASAL SPRAY  
2.7 mg

**FOR USE IN THE NOSE ONLY  
DO NOT TEST BEFORE USE**

Use for known or suspected opioid overdose  
in adults and children 12 years of age and older.

Two Unit-Dose Nasal Spray Devices

Each unit-dose nasal spray device delivers  
2.7 mg nalmefene in 0.1 mL solution.

**EACH DEVICE SPRAYS ONCE ONLY.**

For more information about  
OPVEE Nasal Spray, go to  
[www.OPVEE.com](http://www.OPVEE.com) or 1-877-782-6966

Check product expiration date before use.

20-624 002



700729-02

NDC 12496-0003-2  
Rx only

**OPVEE®**  
(nalmefene)  
**NASAL SPRAY**  
**2.7 mg**

GTIN: 00372496000328

700729-02



**3. Give a dose in the nose**

- Provide support behind the neck with your hand and tilt the person's head back.
- Gently insert the nozzle into one nostril until your fingers on either side of the nozzle are against the bottom of the person's nose.
- Push the plunger firmly all the way down until it stops to give a dose.



**4. Call 911 and place person on their side**

- Call 911 or get emergency medical help right away.
- Move the person on their side (recovery position).
- Stay with the person until medical help arrives.



**5. Watch and give another dose**

- Wait 2 to 5 minutes to see if the person wakes up.
- If the person does not wake up:
  - Get a new OPVEE nasal spray from the box.
  - Give another dose in the other nostril.
  - If more OPVEE nasal sprays are available, repeat Steps 1 through 3 every 2 to 5 minutes, alternating nostrils, until the person wakes up or medical help arrives.



**OPVEE®**  
(nalmefene)  
**NASAL SPRAY**  
**2.7 mg**

**FOR USE IN THE NOSE ONLY  
DO NOT TEST BEFORE USE**

Store at controlled room temperature 15°C to 25°C (59°F to 77°F). Short-term excursions permitted between 4°C to 40°C (39°F to 104°F).

Do not freeze. Protect from light.

Dosage and administration: See prescribing information

**Warning: Keep out of reach of children**

Do not use if nasal spray device appears damaged.



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NDC 12496-0003-2  
Rx only

**OPVEE®**  
(nalmefene)  
**NASAL SPRAY**  
**2.7 mg**

**FOR USE IN THE NOSE ONLY  
DO NOT TEST BEFORE USE**

Use for known or suspected opioid overdose in adults and children 12 years of age and older.

Two Unit-Dose Nasal Spray Devices

Each unit-dose nasal spray device delivers

2.7 mg nalmefene in 0.1 mL solution.

**EACH DEVICE SPRAYS ONCE ONLY.**

For more information about OPVEE Nasal Spray, go to [www.OPVEE.com](http://www.OPVEE.com) or 1-877-782-6966

Check product expiration date before use.

700729-02

**OPVEE®**  
(nalmefene)  
**NASAL SPRAY**  
**2.7 mg**

**FOR USE IN THE NOSE ONLY  
DO NOT TEST BEFORE USE**

Each unit-dose nasal spray device delivers 2.7 mg nalmefene (equivalent to 3 mg

NDC 12496-0003-2  
Rx only

**OPVEE®**  
(nalmefene)  
**NASAL SPRAY**  
**2.7 mg**

**FOR USE IN THE NOSE ONLY  
DO NOT TEST BEFORE USE**

Use for known or suspected opioid overdose in adults and children 12 years of age and older.

- **Important:** OPVEE nasal spray is for use **in the nose only**.
- **Do not remove or test** OPVEE nasal spray before use.
- Each OPVEE nasal spray has 1 dose and cannot be reused.
- You do not need to prime OPVEE nasal spray.



**1. Check for response**

- **Shout** "wake up" and **shake** the person gently.
- If there is no response, slow breathing, or no breathing, **lay the person flat on their back**.

are for how to use

2.7 mg nalmefene (equivalent to 0.1 mg nalmefene HCl) in 0.1 mL solution.  
Inactive ingredients: Benzalkonium chloride, disodium edetate, dodecylmaltoside, purified water, sodium chloride

INDIVIOR<sup>®</sup> Manufactured for Indivior Inc., North Chesterfield, VA 23235, USA

AFFIX PHARMACY LABEL HERE

Two Unit-Dose 2.7 mg Nasal Spray Devices.

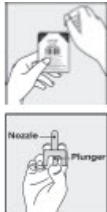
**TWO PACK**  
Each carton contains Instructions for Use.

Check product expiration date before use.

**Open here**

**2. Prepare**

- Remove OPVEE nasal spray from the box.
- Peel off the back from the top corner to open the OPVEE nasal spray blister.
- Hold the OPVEE nasal spray with your fingers on both sides of the nozzle and your thumb on the white plunger.
- Do not press the plunger yet.**



## OPVEE

nalmefene hydrochloride spray

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:12496-0003
<b>Route of Administration</b>	NASAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>nalmefene hydrochloride</b> (UNII: K7K69QC05X) (nalmefene - UNII:TOV02TDP9I)	nalmefene	2.7 mg in 100 uL

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:12496-0003-2	2 in 1 CARTON	10/02/2023	
1	NDC:12496-0003-1	1 in 1 BLISTER PACK		
1		100 uL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217470	10/02/2023	

**Labeler** - Indivior Inc. (797408549)

