Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Narcan 1.8 mg Nasal Spray, solution in a single dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.1 mL dose contains naloxone hydrochloride dihydrate equivalent to 1.8 mg naloxone.

Excipient with known effect
Benzalkonium chloride 0.01 mg per dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal Spray, solution in single dose container.

A clear or colourless or slightly yellow, buffered solution intended for nasal administration

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Narcan is intended for emergency reversal of respiratory and/or central nervous system depression induced by or suspected to be induced by opioids (natural or synthetic), in healthcare settings and in non-medical settings by appropriately trained individuals.

Narcan is indicated for use in adults only.

Narcan is not a substitute for emergency medical care.

4.2 Posology and method of administration

Posology
Narcan may be made available once the prescriber has assessed the suitability and competence of an individual to administer naloxone in the appropriate circumstances.

Narcan may need to be used in a non-medical setting. Therefore, the prescriber as per local clinical guidance should take appropriate steps to ensure that the patient thoroughly understands the indications and use of Narcan.

The choice of a 1.8 mg or 3.6 mg dose depends on the specific particulars of each case and the following factors should be taken into account: the type and amount of opioid which has been taken, patient co-morbidities and concomitant drug or alcohol usage. In opioid-dependent patients expected to be at risk of severe opioid withdrawal, Narcan 1.8 mg should be administered. Subjects believed to have taken high potency opioids such as fentanyl should be administered the 3.6 mg dose, as they may require larger doses of Narcan in order to achieve a response. In cases where a patient has not responded (i.e. does not wake to voice or touch, or is not breathing normally) after receiving a single 1.8 mg dose, switching to the 3.6 mg dose should be considered.

Adults
One actuation into a single nostril.

If a patient does not respond to the first dose of Narcan Nasal Spray after two to three minutes, additional doses may be administered. Administer Narcan Nasal Spray in the alternate nostril with each dose.

If the patient responds to the first dose, but subsequently relapses into respiratory depression, additional doses may be administered.

Children (under 18 years of age)
Narcan Nasal Spray has not been studied in this patient population.

Older People (over 65 years of age)
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 naloxone hydrochloride can be higher in these patients.

Method of administration
Narcan Nasal Spray is for administration by the nasal route only.

Do not prime the spray device before use.

Place the patient in the supine position to receive a dose of Narcan nasal spray. Provide support to the back of the neck to allow the head to tilt back. The spray device should be held with the thumb on the bottom of the plunger and the first and middle finger on either side of the nozzle. The tip of the nozzle should be inserted into either of the patient's nostril. The dose is administered by pressing firmly on the plunger.

Narcan Nasal Spray should not be used prophylactically.

Each Narcan Spray device can only be used one time.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Use by individuals in the community
Narcan is intended as an emergency treatment and the patient should be advised to seek medical help immediately and before Narcan administration. Narcan is not a substitute for emergency medical care. Additional measures to ensure airway patency, respiratory support and/or full cardiopulmonary resuscitation should not be delayed and employed as appropriate.Following administration, stay with the patient and continue to monitor their condition until the arrival of the emergency services.

Patients or any other person who might be in a position to administer Narcan must be instructed in its proper use and the importance of seeking medical assistance Narcan is intended to be administered as a part of a resuscitation intervention in suspected overdose casualties, where opioid drugs may be involved or suspected, likely in a non-medical setting. Therefore, the prescriber should take appropriate steps to ensure that the patient and/or any other person who might be in a position to administer Narcan thoroughly understands the indications and use of Narcan.

The prescriber should describe the symptoms which allow presumptive diagnosis of central nervous system (CNS)/respiratory depression, the indication and the instructions for use with the patient and/or person who might be in a position to administer this product to a patient experiencing a known or suspected opioid overdose event. This should be performed in accordance with the educational guidance for Narcan.

Duration of effect
The duration of action of most opioids may exceed that of Narcan Nasal Spray resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Therefore, it is necessary to keep the patient under continued surveillance after administration of Narcan Nasal Spray until emergency help has arrived. Additional doses may be given every 2-3 minutes if the patient is not adequately responding or responds and then relapses back into respiratory depression.

Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Respiratory depression caused by mixed agonist/antagonists, such as buprenorphine and pentazocine; may require higher doses of naloxone or reversal may be incomplete; if incomplete response occurs, respirations should be mechanically assisted as clinically indicated.

Opioid withdrawal symptoms
The use of Narcan Nasal Spray in patients who are opioid dependent may precipitate an acute withdrawal syndrome characterized by the following signs and symptoms: body aches, diarrhoea, 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 naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary oedema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects should be monitored for hypotension, ventricular tachycardia or fibrillation, and pulmonary oedema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary oedema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary oedema, 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.

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.

In elderly patients with pre-existing cardiovascular disease or in those receiving potentially cardiotoxic drugs, Narcan should be used with caution since serious adverse cardiovascular effects such as ventricular tachycardia and fibrillation have occurred in postoperative patients following administration of naloxone hydrochloride.

Benzalkonium chloride
This medicine contains benzalkonium chloride, which may cause irritation or swelling inside the nose, especially if used for a long time.

4.5 Interaction with other medicinal products and other forms of interactions

Naloxone is an opioid and competitively competes with agonist opioids for opioid receptors and particularly mu receptors, responsible for analgesia and respiratory depression. When administered to subjects dependent on opioids, in some subjects the administration of naloxone hydrochloride can cause pronounced withdrawal symptoms (see section 4.4).

When administering naloxone hydrochloride to patients who have received buprenorphine as an analgesic, complete analgesia may be restored. It is thought that this effect is a result of the arch-shaped dose-response curve of buprenorphine with decreasing analgesia in the event of high doses. However, reversal of respiratory depression caused by buprenorphine may be limited.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no adequate data from the use of naloxone in pregnant women. Studies in animals have shown reproductive toxicity only at maternally toxic doses (see section 5.3). The potential risk for humans is unknown. Narcan should not be used during pregnancy unless the clinical condition of the woman requires treatment with naloxone.

In pregnant women who have been treated with Narcan, the fetus should be monitored for signs of distress.

In opioid dependent pregnant women, naloxone administration can cause withdrawal symptoms in newborn infants (see section 4.4).

Breast feeding
It is unknown whether naloxone is excreted in human breast milk and it has not been established whether infants who are breast fed are affected by naloxone. However, as naloxone is practically not orally bioavailable its potential to affect a breast fed infant is negligible. Caution should be exercised when naloxone is administered to a breast feeding mother but there is no need to discontinue breast feeding. Breast fed babies from mothers who have been treated with Narcan should be monitored to check for sedation or irritability.

Fertility
No clinical data on effects of naloxone on fertility are available, however data from rat studies (see section 5.3) indicate no effects.

4.7 Effects on ability to drive and use machines

Patients who have received naloxone hydrochloride to reverse the effects of opioids should be warned not to drive, to operate machinery or to engage in other activities demanding physical or mental exertion for at least 24 hours, since the effect of the opioids may return.

4.8 Undesirable effects

The following frequency terminology is used:
Very common: ≥1/10;
Common: ≥1/100 to <1/10;
Uncommon: ≥1/1,000 to <1/100;
Rare: ≥1/10,000 to <1/1000;
Very rare: <1/10,000;
Not known (cannot be established from the available data)

Adverse events associated with nasal naloxone in clinical trials and from post marketing experience
In a pharmacokinetic study of 30 healthy adult volunteers exposed to one spray of nasal naloxone in one nostril or two sprays of nasal naloxone, one in each nostril, the adverse events reported were: erythema and oedema of nasal mucosa, nasal pain, headache.

Presented below are adverse events that have been reported in association with the use of injectable naloxone.

System Organ Class	Adverse Event	Frequency
Immune system disorders	Allergic reactions (urticaria, rhinitis, dyspnoea, Quincke's oedema) Anaphylactic shock	Very rare Very rare
Nervous system disorders	Dizziness Headache Tremor Sweating Seizures Tension Seizures have occurred rarely following administration of naloxone hydrochloride; however, a causal relationship to the drug has not been established. Higher than recommended dosage in postoperative use can lead to tension.	Common Common Uncommon Uncommon Rare Rare
Cardiac disorders	Tachycardia Arrhythmia Bradycardia Fibrillation Cardiac arrest	Common Uncommon Uncommon Very rare Very rare
Vascular disorders	Hypotension Hypertension Hypotension, hypertension and cardiac arrhythmia	Common Common

	(including ventricular tachycardia and fibrillation) have also occurred with the postoperative use of naloxone hydrochloride. Adverse cardiovascular effects have occurred most frequently in postoperative patients with a pre-existing cardiovascular disease or in those receiving other drugs that produce similar adverse cardiovascular effects.	
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema Pulmonary oedema has also occurred with the postoperative use of naloxone hydrochloride Runny nose, sneezing, yawning	Very rare Not known
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Dry mouth Nausea and vomiting have been reported in postoperative patients who have received doses higher than recommended. However, a causal relationship has not been established, and the symptoms may be signs of too rapid antagonisation of the opioid effect.	Very common Common Uncommon Uncommon
Skin and subcutaneous tissue disorders	Erythema multiforme One case of erythema multiforme cleared promptly after naloxone hydrochloride was discontinued.	Very rare
General disorders and administration site conditions	Postoperative pain Hyperventilation Irritation of vessel wall (after i.v. administration) Local irritation and inflammation (after i.m. administration) Higher than the recommended dosage in postoperative use can lead to the return of pain. A fast reversal of opioid effect can induce hyperventilation.	Common Uncommon Uncommon Uncommon
Infections and infestations	Fever	Not known
Investigations	Increased blood pressure when reversal of opioid depression is abrupt	Not known
Injury, poisoning and procedural complications	Agitation when administered in excessive doses to postoperative patients	Not known
Surgical and medical procedures	Reversal of analgesia when administered in excessive doses to postoperative patients	Not known
Musculoskeletal and connective tissue disorders	Weakness Shivering	Not known Not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

In view of the indication and the broad therapeutic margin, overdose is not to be expected. Single doses of intravenous 10 mg naloxone hydrochloride have been tolerated without any adverse effects or changes in laboratory values. Higher than recommended dosage in postoperative use can lead to the return of pain and tension.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidotes

ATC-Code: V03AB15

Naloxone hydrochloride, a semi synthetic morphine derivative (N-allyl-nor-oxymorphone), is a specific opioid antagonist that acts competitively at opioid receptors. It reveals very high affinity for the opioid receptor sites and therefore displaces both opioid agonists and partial antagonists, such as pentazocine, for example, but also nalorphine. Naloxone hydrochloride does not counteract central depression caused by hypnotics or other non-opioids and does not possess the agonistic or morphine-like properties characteristic of other opioid antagonists. In the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

In case of opioid dependence, administration of naloxone hydrochloride will enhance the symptoms of physical dependence. The need for repeated doses depends on the quantity, type and route of administration of the opioid to be antagonised.

5.2 Pharmacokinetic properties

Absorption
Following intranasal administration of 4 mg naloxone hydrochloride, a peak plasma concentration of 5.3 ng/mL occurred approximately 0.5 hour (range 0.2, 1.00) following administration, and with an $AUC_{0-\infty}$ of 8.5 ng*hr/mL. Intranasal administration of 2 mg naloxone hydrochloride resulted in a peak plasma concentration of 3.1 ng/mL at 0.3 hour (range 0.3, 1.0) with an $AUC^{0-\infty}$ of 4.7 ng*hr/mL. The relative bioavailability of naloxone following intranasal administration compared to intramuscular naloxone was approximately 50%.

Distribution
Following parenteral administration, naloxone hydrochloride is rapidly distributed into body tissues and fluids, especially into the brain, because the drug is highly lipophilic. In adult humans, the distribution volume at steady-state is reported to be about 2 l/kg. Protein binding is within the range of 32 to 45 %. Naloxone hydrochloride readily crosses the placenta; however, it is not known whether naloxone hydrochloride is distributed into breast milk.

Biotransformation
Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucoronide as the major metabolite.

Elimination
After an oral or intravenous dose, about 25-40% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours. Following administration of nasal naloxone(single 4 mg and 2 mg dose of naloxone hydrochloride nasal spray, respectively), the mean plasma half-life of naloxone in healthy adults was approximately 2.2 and 1.9 hours, respectively. In a neonatal study of naloxone hydrochloride injection, the mean (± SD) plasma half-life was observed to be 3.1 hours.

5.3 Preclinical safety data

Naloxone was not mutagenic in the bacterial reverse mutation assay, but was positive in mouse lymphoma assay and was clastogenic *in vitro*, however, naloxone was not clastogenic *in vivo*.

Naloxone had no effect on fertility and reproduction in the rat or on early embryonic development of the rat and rabbit. In peri-post natal rat studies, naloxone produced increased pup deaths in the immediate post-partum period at the high doses

that also caused significant maternal toxicity in rats (e.g. bodyweight loss, convulsions). Naloxone did not affect development or behaviour of surviving pups. Naloxone is therefore not teratogenic in rats or rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Sodium chloride
Hydrochloric acid (for pH adjustment)
Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Narcan Nasal Spray is supplied in Type 1 glass vials sealed with chlorobutyl rubber plungers and enclosed within a spray device.

Each unit dose spray device containing 0.1 ml solution is presented in an individually sealed blister.

Packs contain two blisters.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Remove the spray device from the blister pack. Place the patient in the supine position, and provide support to the back of the neck to allow the head to tilt back. The spray device should be held with the thumb on the bottom of the plunger and the first and middle finger on either side of the nozzle. The tip of the nozzle should be inserted into either of the patient's nostril. The dose is administered by pressing firmly on the plunger.

Dispose of the used empty Narcan nasal spray device in a location that is protected from children.

7 MARKETING AUTHORISATION HOLDER

Emergent Operations Ireland Limited
6th Floor
6 Earlsfort Terrace
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2162/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd March 2018

10 DATE OF REVISION OF THE TEXT

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