Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ventizolve 1.26 mg nasal spray, solution in single-dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nasal spray container delivers 1.26 mg of naloxone (as hydrochloride dihydrate).

Excipient with known effect
One dose delivers 20 microgram benzalkonium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, solution (nasal spray).

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ventizolve is intended for immediate administration as emergency therapy for known or suspected opioidoverdose as manifested by respiratory and/or central nervous system depression, in both non-medicaland healthcare settings.

Ventizolve is indicated in adults.

Ventizolve is not a substitute for emergency medical care.

4.2 Posology and method of administration

Posology

Adults
The recommended dose is 1.26 mg administered into one nostril (one nasal spray).

If respiration is stabilized the patient should be monitored and placed in the recovery position until health care professionals (HCP) are on site.

Ventizolve is administered in opioid-dependent subjects, especially when expected to be at risk of severe opioid withdrawal. In some cases, further doses may be necessary. The appropriate maximum dose of Ventizolve is situation specific. If the patient does not respond, the second dose should be administered after 2-3 minutes. If the patient responds to the first administration but then relapses again into respiratory depression, the second dose should be administered immediately. Further doses (if available) should be administered in alternate nostrils and the patient should be monitored whilst awaiting arrival of the emergency services.

Paediatric population
The safety and efficacy of Ventizolve in children and adolescents has not been established. No data are available.

Elderly
No adjustment of dose is required.

Method of administration
Nasal use.

Ventizolve should be administered as soon as possible to avoid damage to the central nervous system or death.

Detailed instructions on how to use Ventizolve are provided in the Package Leaflet.

The device contains only one dose. Do not prime or test the device prior to administration. Do not reuse the device after administration.

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

Instructing patients /users on the proper use of Ventizolve
Ventizolve 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 healthcare professional should take appropriate steps to ensure that the patient and/or any other person who might be in a position to administer Ventizolve thoroughly understands the indications and use of Ventizolve.

The healthcare professional 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 Ventizolve.

Ventizolve contains one single dose of naloxone. Patients and care takers should therefore receive proper instructions on how to use the device, and that it should not be primed or tested prior to administration and that it cannot be reused after administration of the dose (see section 4.2).

Monitoring of the patient for a response
Administer additional doses as necessary, if the patient is not adequately responding or responds and then relapses back into respiratory depression. See section 4.2.

The importance of seeking medical assistance
Patients should be kept under observation until qualified healthcare personnel are on site. The duration of action of most opioids may exceed that of Ventizolve resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Therefore, it is necessary to seek emergency medical assistance immediately and to keep the patient under continued surveillance.

Effectiveness of naloxone
Naloxone is not effective against CNS- or respiratory depression caused by non-opioid drugs. Reversal of respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and may require higher doses of naloxone hydrochloride or repeated administrations. Intranasal absorption and efficacy of naloxone can be altered in patients with damaged nasal mucosa and septal defects. If an incomplete response occurs, respiration should be mechanically assisted.

Opioid withdrawal syndrome
Abrupt reversal of opioid effects in persons who are physically dependent on opioids can precipitate an acute withdrawal syndrome. The severity and duration of the withdrawal relate to the dose of naloxone and the degree and type of opioid dependency. See section 4.8. Patients who are receiving opioids for the relief of chronic pain may experience pain and opioid withdrawal symptoms when Ventizolve is administered.

Ventizolve contains the preservative benzalkonium chloride. Benzalkonium chloride 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 interaction

Naloxone elicits a pharmacological response due to the interaction with opioids and opioid agonists.There is no interaction with barbiturates or tranquillizers when using standard doses of naloxone hydrochloride. When administered to opioid dependent subjects, naloxone can cause acute withdrawal symptoms insome individuals. Hypertension, cardiac arrhythmias,

pulmonary oedema and cardiac arrest have beendescribed, more typically when naloxone is used post-operatively (see sections 4.4 and 4.8).

Administration of naloxone may decrease the analgesic effects of opioids used primarily to provide pain relief, due to its antagonist properties (see section 4.4).

In patients receiving buprenorphine for analgesic purposes, full analgesic effect of buprenorphine may be restored by administration of naloxone. It is thought that this effect is a result of the arch-shaped dose-responsecurve of buprenorphine with decreasing analgesia in the event of high doses. Reversal of respiratory depression caused by buprenorphine is however limited.

Data regarding interaction with alcohol are not clear. Depending on the cause of intoxication, the effect following administration of naloxone may be delayed in patients with multi-intoxications effected by opioids and sedatives or alcohol.

Serious hypertension has been reported with use of naloxone in cases of coma caused by clonidine overdose.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of naloxone in pregnant women. Studies in animals have shown reproductive toxicity only at maternally toxic doses. The potential risk to humans is not known. Ventizolve should not be used during pregnancy unless the clinical condition of thewoman requires treatment with naloxone.

In pregnant women who have been treated with Ventizolve, the fetus should be monitored for signs ofdistress.

Breastfeeding
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 breastfeeding mother, but there is no need to discontinue breastfeeding. Breast-fed babies from mothers who have been treated with Ventizolve should bemonitored 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 to reverse the effects of opioids should be warned not to take part in road traffic, 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

Summary of the safety profile
The most common adverse drug reaction (ADR) seen with naloxone administration is nausea (frequency very common). Abrupt reversal of opioid effects in persons who are physically dependent on opioids can precipitate an acute withdrawal syndrome.

Tabulated list of adverse reactions
The following adverse reactions have been reported with Ventizolve and/or other naloxone-containingmedicinal products during clinical studies and post marketing experience. ADRs are listed below bysystem organ class and frequency.

Frequency categories are assigned to those adverse reactions considered to be at least possibly causally related to naloxone and are defined as very common: (≥ 1/10); common: (≥ 1/100 to < 1/10); uncommon: (≥ 1/1,000 to < 1/100); rare: (≥ 1/10,000 to < 1/1,000) very rare: (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Adverse reactions
Immune system disorders	
Very rare:	Hypersensitivity, anaphylactic shock
Nervous system disorders	
Common:	Dizziness, headache
Uncommon:	Tremor
Cardiac disorders	
Common:	Tachycardia
Uncommon:	Arrhythmia, bradycardia
Very rare:	Cardiac fibrillation, cardiac arrest
Vascular disorders	
Common:	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Hyperventilation
Very rare:	Pulmonary oedema
Gastrointestinal disorders	
Very common:	Nausea
Common:	Vomiting
Uncommon:	Diarrhoea, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Hyperhidrosis
Very rare:	Erythema multiforme
General disorders and administration site conditions	
Uncommon:	Drug withdrawal syndrome (in patients dependent on opioids)

Description of selected adverse reactions

Drug withdrawal syndrome

Signs and symptoms of drug withdrawal syndrome include restlessness, irritability, hyperaesthesia, nausea, vomiting, gastrointestinal pain, muscle spasms, dysphoria, insomnia, anxiety, hyperhidrosis, piloerection, tachycardia, increased blood pressure, yawning, pyrexia. Behavioural changes including violent behaviour, nervousness and excitement may also be observed.

Vascular disorders

In reports on intravenous/intramuscular naloxone: hypotension, hypertension, cardiac arrhythmia (including ventricular tachycardia and fibrillation) and pulmonary oedema have occurred with the postoperative use of naloxone. Adverse cardiovascular effects have occurred more frequently in postoperative patients with a pre-existing cardiovascular disease or in those receiving other medicines that produce similar adverse cardiovascular effects.

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 676497 ; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Overdose is not expected considering the indication and the broad therapeutic index. Single doses of 10 mg naloxone administered intravenously has been tolerated without adverse reactions or changes in clinical laboratory values.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidotes, ATC code: V03AB15

Mechanism of action
Naloxone is a semi-synthetic morphine derivative (N-allyl-noroxymorphon) and a specific opioid antagonist that antagonises opioid effects by competing for the same receptor sites. The effect is due to antagonism of mu, kappa, delta opioid receptors. The antagonism of the mu receptor restores respiration.

Pharmacodynamic effects
Naloxone reverses the effects of opioids, including respiratory depression, sedation, and hypotension. It has a very high affinity to opioid receptors and as a result displaces both opioid agonists and partial antagonist like e.g. pentazocine and nalorphine. Naloxone does not reverse CNS depression caused by hypnotics or other non-opioids and does not have agonistic or morphine-like effects as other opioid antagonists.

In cases of opioid dependency, administration of naloxone will increase the symptoms of physical dependency. The pharmacological effects of naloxone will typically be observed within 2 minutes following administration. The duration of the antagonistic effect is dose dependant but is typically 1-4 hours. The need for repeated dosing depends on the amount, type and route of administration of the opioid to be antagonised.

5.2 Pharmacokinetic properties

Absorption
In a pharmacokinetic study in 22 healthy adult subjects, the relative bioavailability of one nasal spray in one nostril (1.4 mg total dose naloxone hydrochloride, equivalent to 1.26 mg naloxone base, given as 0.1 ml of 14 mg/ml naloxone hydrochloride) and two nasal sprays administered in the same nostril (2.8 mg total dose naloxone hydrochloride, equivalent to two times 1.26 mg naloxone base, given as 2 x 0.1 ml of 14 mg/ml naloxone hydrochloride) was compared to a single dose of 0.8 mg naloxone hydrochloride intramuscular injection and 0.4 mg naloxone hydrochloride intravenous injection. Absolute bioavailability of the nasal spray was on average 0.49 ±0.24. Results are presented in Table 1 below.

Table 1. Mean pharmacokinetic parameters for naloxone following administration of Ventizolve, intramuscular and intravenous naloxone hydrochloride to healthy subjects.

Parameter	**1.4 mg/dose intranasal – one dose**	**1.4 mg/dose intranasal – two doses**	**0.8 mg intramuscular injection**	**0.4 mg intravenous injection**
tmax (min)	20.16	20.7	13.62	3.48*
Cmax (ng/ml)	2.356	4.181	3.734	7.437*
AUC0-last (h*ng/ml)	2.622	5.232	3.091	1.839
AUC0-inf (h*ng/ml)	2.842	5.469	3.431	2.087
t1/2 (h)	1.216	1.162	1.414	1.239
Dose normalised relative bioavailability (%) IN vs. IM	0.52			

* Time and concentration at first sampling point = 2 minutes

Mean plasma concentrations of naloxone after 2 and 5 minutes following 1.4 mg IN Ventizolve were 0.5475 ng/mL (23% of Cmax) and 0.9519 ng/mL (40% of Cmax), respectively. Onset of action following intranasal administration can reasonably be expected to occur in each individual before the tmax is reached. The corresponding mean plasma concentrations of naloxone after 2 and 5 minutes following 0.8 mg IM naloxone were 1.4979 ng/mL (40% of Cmax) and 3.1551 ng/mL (85% of Cmax), respectively.

Distribution
Naloxone is a highly lipophilic compound and following parenteral administration it is rapidly and extensively distributed into body fluids and tissues including the brain. Naloxone readily crosses the placenta. It is not known whether naloxone is excreted into human milk.
Plasma protein binding occurs but is relatively weak (32-45%). Plasma albumin is the major binding constituent, but significant binding of naloxone also occurs to plasma constituents other than albumin.

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

Elimination
In adults, the elimination half-life is approximately 1 to 1.5 hours after parenteral administration. In a pharmacokinetic study, there was no significant difference in elimination following administration of Ventizolve and 0.8 mg IM and 0.4 mg IV formulations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity.

Genotoxicity and carcinogenicity
Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.
Overall, the weight of evidence indicates that naloxone poses minimal, if any, risk for human genotoxicity and carcinogenicity.

Reproductive and developmental toxicity
Naloxone had no effect on fertility and reproduction in the rat, or on early embryonic development of the rat and mouse. Naloxone is not teratogenic in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Glycerol
Disodium edetate
Benzalkonium chloride
Citric acid monohydrate
Sodium citrate
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not freeze.

Keep the single-dose containers in the plastic cover in order to protect from light.
Keep the blister packs in the outer carton in order to protect from light.

6.5 Nature and contents of container

The immediate container consists of a type I glass vial with a chlorobutyl rubber stopper enclosed in a spray device comprised of polypropylene actuator and spray pin and a stainless steel cannula.

Pack sizes:
Carton with 1 plastic cover contains 2 single-dose containers of 0.1 ml nasal spray.
Carton with 10 plastic covers each containing 2 single-dose containers of 0.1 ml nasal spray.
Carton with 6 blister packs each containing 1 single-dose container of 0.1 ml nasal spray.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Navamedic ASA
Henrik Ibsens Gate 100
Oslo
0255
Norway

8 MARKETING AUTHORISATION NUMBER

PA1270/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd February 2019
Date of last renewal 14th June 2023

10 DATE OF REVISION OF THE TEXT

February 2026