SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nyxoid 1.8 mg nasal spray, solution in single-dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nasal spray container delivers 1.8 mg of naloxone (as hydrochloride dihydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, solution in single-dose container (nasal spray)

Clear, colourless to pale yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nyxoid is intended for immediate administration as emergency therapy for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression in both non-medical and healthcare settings.

Nyxoid is indicated in adults and adolescents aged 14 years and over.

Nyxoid is not a substitute for emergency medical care.

4.2 Posology and method of administration

Posology

Adults and adolescents aged 14 years and over

The recommended dose is 1.8 mg administered into one nostril (one nasal spray).

In some cases, further doses may be necessary. The appropriate maximum dose of Nyxoid 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. Emergency services may administer further doses according to local guidelines.

Paediatric population

The safety and efficacy of Nyxoid in children below 14 years has not been established. No data are available.

Method of administration

Nasal use.

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

Nyxoid contains only one dose and therefore it must not be primed or tested prior to administration.

Detailed instructions on how to use Nyxoid are provided in the Package Leaflet and a Quick Start Guide is printed on the back of each blister. In addition, training is provided via a video and a Patient Information Card.

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 Nyxoid

Nyxoid should only be made available once the suitability and competence of an individual to administer naloxone in the appropriate circumstances has been established. Patients or any other person who might be in a position to administer Nyxoid must be instructed in its proper use and the importance of seeking medical assistance.

Nyxoid is not a substitute for emergency medical care and may be used instead of intravenous injection, when intravenous access is not immediately available.

Nyxoid 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 Nyxoid thoroughly understands the indications and use of Nyxoid.

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 Nyxoid.

Monitoring of the patient for a response

Patients who respond satisfactorily to Nyxoid must be closely monitored. The effect of some opioids can be longer than the effect of naloxone, which could lead to reoccurrence of respiratory depression and therefore further doses of naloxone may be required.

Opioid withdrawal syndrome

Receiving Nyxoid can lead to a rapid reversal of the opioid effect which can cause an acute withdrawal syndrome (see section 4.8). Patients who are receiving opioids for the relief of chronic pain may experience pain and opioid withdrawal symptoms when Nyxoid is administered.

Effectiveness of naloxone

Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs, respiration should be mechanically assisted.

Intranasal absorption and efficacy of naloxone can be altered in patients with damaged nasal mucosa and septal defects.

Paediatric population

Opioid withdrawal may be life-threatening in neonates if not recognised and properly treated and may include the following signs and symptoms: convulsions, excessive crying and hyperactive reflexes.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

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. When administered to opioid dependent subjects, naloxone can cause acute withdrawal symptoms in some individuals. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest have been described, more typically when naloxone is used post-operatively (see sections 4.4 and 4.8).

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

When administering naloxone 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 is limited.

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 (see section 5.3). The potential risk for humans is unknown. Nyxoid 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 Nyxoid, 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 Nyxoid 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 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

Summary of the safety profile

The most common adverse reaction (AR) seen with naloxone administration is nausea (frequency very common). Typical opioid withdrawal syndrome is expected with naloxone which may be caused by the abrupt withdrawal of opioid in persons physically dependent on them.

Tabulated list of adverse reactions

The following adverse reactions have been reported with Nyxoid and/or other naloxone-containing medicinal products during clinical studies and post marketing experience. ARs are listed below by system 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, < 1/10); uncommon: (≥ 1/1,000, < 1/100); rare: (≥ 1/10,000, < 1/1,000) very rare: (< 1/10,000); not known (cannot be estimated from the available data).

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 medicinal products that produce similar adverse cardiovascular effects.

Paediatric population

Nyxoid is intended for use in adolescents 14 years and over. Frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In view of the indication and the broad therapeutic margin, overdose is not to be expected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidotes, ATC code: V03AB15

Mechanism of action and pharmacodynamic effects

Naloxone, a semisynthetic 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. Naloxone 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. Naloxone has not been shown to produce tolerance or cause physical or mental dependence.

As the duration of action of some opioid agonists may be longer than that of naloxone, the effects of the opioid agonist may return as the effects of naloxone disappear. This may necessitate repeat doses of naloxone – though the need for repeat naloxone doses is dependent on the quantity, type and route of administration of the opioid agonist that is being treated.

Paediatric population

No data are available.

5.2 Pharmacokinetic properties

Absorption

Intranasal administration of naloxone has demonstrated naloxone to be rapidly absorbed, as evidenced by very early appearance (as early as 1 minute after administration) of the active substance in systemic circulation.

A study investigating intranasal naloxone at doses of 1, 2, 4 mg (MR903-1501) shows that the median (range) t_{max} associated with intranasal administration of naloxone was 15 (10, 60) minutes for 1 mg, 30 (8, 60) minutes for 2 mg and 15 (10, 60) minutes for 4 mg intranasal doses. Onset of action following intranasal administration can reasonably be expected to occur in each individual before the t_{max} is reached.

The half value duration (HVD) values for intranasal administration were longer than for intramuscular administration (intranasal, 2 mg, 1.27h, intramuscular, 0.4 mg 1.09h) from which we can infer a longer duration of action of naloxone given by the intranasal rather than the intramuscular route. If the duration of action of the opioid agonist exceeds that of intranasal naloxone, the effects of the opioid agonist may return, necessitating a second intranasal naloxone administration.

A study demonstrated mean absolute bioavailability of 47% and mean half-lives of 1.4 h from intranasal doses of 2 mg.

Biotransformation

Naloxone is rapidly metabolized in the liver and excreted in the urine. It undergoes extensive hepatic metabolism mainly by glucuronide conjugation. The principal metabolites are naloxone-3-glucuronide, 6-beta-naloxol and its glucuronide.

Elimination

There are no data available on the excretion of naloxone following intranasal administration, however, the disposition of labelled naloxone following intravenous administration was studied in healthy volunteers and opioid-dependent patients. Following an intravenous dose of 125 µg, 38% of the dose was recovered in the urine within 6 hours in healthy volunteers compared with 25% of the dose being recovered in opioid-dependent patients in the same time period. After a period of 72 hours, 65% of the injected dose was recovered in urine in the healthy volunteers compared with 68% of the dose in opiate-dependent patients.

Paediatric population

No data are available.

5.3 Preclinical safety data

Genotoxicity and carcinogenicity

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 was not carcinogenic following oral administration in a rat 2-year study or in a 26-week study in Tg-rasH2 mice. 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 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

Trisodium citrate dihydrate (E331)
Sodium chloride
Hydrochloric acid (E507)
Sodium hydroxide (E524)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

The immediate container consists of a type I glass vial with siliconised chlorobutyl stopper containing 0.1 ml solution. The secondary packaging (actuator) is comprised of polypropylene and stainless steel.

Each pack contains two single-dose nasal sprays.

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

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CB4 0GW
UNITED KINGDOM

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