NYXOID® 1.8mg nasal spray

Naloxone hydrochloride dihydrate

1 PRODUCT NAME

NYXOID® 1.8mg nasal spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 100µl contains 1.8 mg naloxone (as hydrochloride dihydrate).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nasal spray, solution.

NYXOID nasal spray is a clear, colourless to pale yellow solution in glass vials in a single dose nasal spray device

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NYXOID is intended as part of the emergency treatment for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression in:

- the home or other non-medical setting
- a health facility setting

For this reason, NYXOID should be carried by persons at risk of, or likely to witness such events.

NYXOID is indicated in adults and adolescents aged 14 years of age and over.

4.2 Dose and method of administration

NYXOID is administered as a part of a resuscitation intervention in emergency settings, including the home or other non-medical settings in suspected overdose casualties, where opioids may be involved or suspected.

The prescriber should review in detail, the indications, the instructions and operation of the nasal spray with the patient or any other person who might be in a position to administer this product to a patient experiencing a known or suspected opioid overdose event.

How to identify an opioid overdose (symptoms of respiratory depression)

- Breathing problems
- Severe sleepiness
- Not responding to a loud noise or touch.

Dosage

Adults and adolescents aged 14 years and over

One spray of NYXOID into one nostril. Re-administer NYXOID, using a new NYXOID container, into the other nostril after 2 to 3 minutes if the patient does not respond or responds and then relapses into respiratory depression. Further doses may be given every 2 to 3 minutes in alternate nostrils if needed until further assistance is available.

Paediatric population

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

Method of administration

Nasal use only.

NYXOID spray 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.

The device is ready for use.

If an overdose is suspected, call for emergency medical assistance immediately. NYXOID is NOT a substitute for emergency medical care.

How to use NYXOID

NYXOID should be administered as quickly as possible to avoid damage to the central nervous system or death. NYXOID is a **single dose** nasal spray. **Do not test the device as it cannot be reused.**

1.	**Call for emergency help** before giving NYXOID.
2.	Lay the patient on their **back**. Support the back of the neck to allow the **head to tilt back**.
3.	Inspect and clear the nasal airway. Insert the NYXOID nozzle in the patient's nostril. **Press firmly** on the device plunger **until it clicks** to give the dose, then **remove the nozzle** from the nostril.
4.	Lay the patient on their side in the **recovery position** and **stay with them** until the emergency services arrive. Watch for an improvement in the patient's breathing level, alertness and response to noise and touch.
5.	If there is **no improvement**, a **second dose** can be given after **2-3 minutes** in the alternate nostril. The patient can be in the recovery position when they receive further second doses. Once the **patient is breathing** normally, **do not** administer further doses of NYXOID
6.	Further doses may be given every 2 to 3 minutes in alternate nostrils if needed until further assistance is available.

If no improvement is seen in the patient and the person administering NYXOID is appropriately trained, CPR can be given as an additional resuscitation measure.

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 (IV) injection, when IV access is not immediately available.

NYXOID is intended to be administered as a part of a resuscitation intervention in suspected overdose casualties, where opioids may be involved or suspected, including the home or other non-medical settings. 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 Nyxioid (see section 4.2).

The prescriber should describe the symptoms which allow presumptive diagnosis of 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.

The importance of seeking medical assistance

NYXOID is intended as part of an emergency treatment and the patient/carer should be advised to seek medical help immediately. Therefore patients at risk or likely to witness an opioid overdose should be carefully instructed in regard to the circumstances under which this potentially life-saving medicinal product should be used.

Monitoring of the patient for a response

Patients who respond satisfactorily to naloxone 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 naloxone can lead to a rapid reversal of the opioid effect which can cause an acute withdrawal syndrome in such patients (see section 4.8). Patients who are receiving opioids for the relief of chronic pain may experience pain and opioid withdrawal symptoms when naloxone 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.

4.5 Interaction with other medicines 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 cardia 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 antagonistic 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 this effect is the 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 women requires treatment with naloxone.

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

In pregnant women who are opioid dependent, naloxone administration can cause withdrawal symptoms in new-born infants (see section 4.4).

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 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 drug reaction (ADR) seen with naloxone administration is nausea (frequency of 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 reaction

The following adverse reactions have been reported with NYXOID and/or other naloxone-containing products during clinical studies and post marketing experience. ADRs 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 IV/IM 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 drugs that produce similar adverse cardiovascular effects.

Paediatric population

NYXOID is intended for use in adolescents 14 years and over. The 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

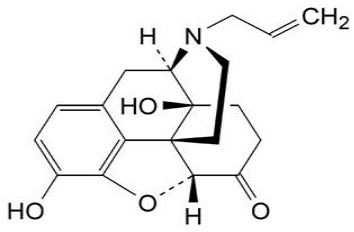
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidotes

ATC code: V03AB15

Naloxone hydrochloride is an off-white powder soluble in water. The chemical name is 17-allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate (CAS No.: 51481-60-8). It is a synthetic congener of oxymorphone, with molecular formula $C_{19}H_{21}NO_4.HCl.2.H_2O$ and molecular weight 399.87. The pKa is 7.9 and the Partition Coefficient Log P is 1.5. The structural formula for naloxone hydrochloride is:



, HCl , 2 H_2O

No clinical trials have been conducted with NYXOID. Efficacy has been inferred based on pharmacokinetic studies.

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.

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 IM administration (intranasal, 2 mg, 1.27h, IM, 0.4 mg, 1.09h) from which we can infer a longer duration of action of naloxone given by the IN rather than the IM route. If the duration of action of the opioid agonist exceeds that of IN 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 the intranasal doses of 2 mg.

Biotransformation

Naloxone is rapidly metabolised 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 IN administration, however, the disposition of labelled naloxone following IV administration was studied in healthy volunteers and opioid-dependent patients. Following an IV 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.

5.3 Preclinical safety data

Genotoxicty 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 development toxicity

Naloxone had no effect on fertility and reproduction in the rat or on early embryonic development of the rat. 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

Sodium citrate dihydrate

Sodium chloride

Hydrochloric acid

Sodium hydroxide

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze.

6.5 Nature and contents of container

The container consists of a type I Ph.Eur. glass vial with chlorobutyl stopper and polypropylene applicator.

NYXOID 1.8 mg nasal spray: unit dose spray device containing 0.1 ml solution.

Each pack contains two single dose nasal sprays.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Distributed on behalf of Mundipharma New Zealand Limited by:
Pharmaco (N.Z.) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Ph: (09) 377-3336
Toll Free [Medical Enquiries]: 0800 773 310

9 DATE OF FIRST APPROVAL

TBC

10 DATE OF REVISION OF THE TEXT

14 February 2019

[SmPC dated 10 Nov 2017][Orbis NZR-0056]

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	New Data Sheet