AUSTRALIAN PRODUCT INFORMATATION - NYXOID® (NALOXONE HYDROCHLORIDE DIHYDRATE) NASAL SPRAY

1 NAME OF THE MEDICINE

Naloxone hydrochloride dihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 100 microlitre contains 2.2 mg naloxone hydrochloride dihydrate. For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

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 children.

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

One spray of Nyxoid into a 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 if needed until further assistance is available.

Method of administration

Nasal use only.

The device is ready for use. No further assembly or priming is required.

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.
6. Further doses may be given every 2 to 3 minutes 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.

Dosing Modifications due to 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 and require higher doses of naloxone.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Instructing patients / users on the proper use of Nyxoid

Patients or any other person who might be in a position to administer this product must be instructed in the proper use of Nyxoid.

Nyxoid is not a substitution for emergency medical care and cannot replace intravenous injection. It 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 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 plan for Nyxoid. Therefore, patients at risk of experiencing an opioid overdose event and/or any other person who might be in a position to administer Nyxoid to a patient experiencing such an event should be carefully instructed in regard to the circumstances under which this potentially life-saving medicinal product should be used.

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.

The duration of action of most opioids may exceed that of Nyxoid nasal spray resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms.

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 Adverse Effects). Patients who are receiving opioids for the relief of chronic pain may experience pain and opioid withdrawal symptoms when naloxone is administered.

The use of Nyxoid nasal spray in patients who are opioid-dependent may bring about opioid withdrawal characterised 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. If these signs and symptoms occur no further Nyxoid should be given.

Effectiveness of naloxone

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

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine may be incomplete. Larger or repeat doses of naloxone hydrochloride may be required for patients who have taken buprenorphine because it has a long duration of action.

Buprenorphine antagonism is characterised by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

Use in the elderly

No data avialable

Paediatric use

Absorption of naloxone following intranasal administration in paediatric patients may be erratic or delayed. Monitor the paediatric patients for at least 24 hours for the development of the signs and symptoms of opioid withdrawal syndrome even when the patient responds appropriately to naloxone.

Where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of alternative naloxone-containing dosage forms that can be titrated to effect and, where applicable, dosed according to weight.

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.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed with Nyxoid. The effect of naloxone is based on the interaction with opioids and opioid agonists, reversing effects of opioids; rapid reversal may precipitate acute withdrawal syndrome in opioid dependence. At the usual naloxone dose there is no interaction with barbiturates and tranquillisers. Data on the interaction with alcohol are not uniform. In patients with multiple intoxication with opioids and sedatives or alcohol, the result of naloxone administration may be delayed, dependent on the cause of intoxication.

Complete analgesia can be restored following administration of naloxone hydrochloride to patients that had buprenorphine as analgesic. It is assumed that this effect is caused by the arched form of the dose-response curve of buprenorphine with decreasing analgesia at (too) high doses. However, reversal of respiratory depression caused by buprenorphine is limited.

Serious hypertension has been reported following administration of naloxone hydrochloride to patients in a coma caused by clonidine-overdosing.

Naloxone reverses the analgesic and other effects of opioid agonist/ antagonists such as pentazocine, so may precipitate withdrawal symptoms if used concurrently with these medicines in physically dependent patients.

Naloxone reverses the analgesic and other effects of opioid agonist analgesics, and may precipitate withdrawal symptoms if used concurrently with these medicines in physically dependent patients, including patients receiving methadone to treat opioid dependence.

When naloxone is used postoperatively to reverse the central depressive effects of opioid agonists used as anaesthesia adjuncts, the dose of naloxone must be carefully titrated to achieve the desired effect without interfering with control of postoperative pain, or causing other adverse effects.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No clinical data on effects of naloxone on fertility are available, however data from rat studies indicate no effects.

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.

Use in pregnancy – Pregnancy Category B1

Naloxone hydrochloride crosses the placenta and may precipitate withdrawal in the foetus as well as in the opioid-dependent mother. The foetus should be evaluated for signs of distress after Nyxoid nasal spray is used. Careful monitoring is needed until the foetus and mother are stabilised.

There are no adequate data from the use of naloxone in pregnant women. Studies in animals do not show any concerns on reproductive toxicity. The potential risk for humans is unknown. The benefit risk of the medicinal product must be considered before use.

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

Use in lactation

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 nursing mother but there is no need to discontinue breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE OR 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 ADVERSE EFFECTS (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 reactions

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, Sweating
Rare	Seizures, Tension

Cardiac disorders

Common	Tachycardia
Uncommon	Arrhythmia, Bradycardia
Very rare	Cardiac fibrillation, Cardiac arrest

Vascular disorders

Common	Hypotension, Hypertension

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.

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

Common	Post-operative pain
Uncommon	Drug withdrawal syndrome (in patients dependent on opioids), Hyperventilation

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.

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 at www.tga.gov.au/reporting-problems via the national reporting system.

Paediatric population

The frequency, type and severity of adverse reactions in paediatrics are expected to be the same as in adults.

Monitor the paediatric patients for at least 24 hours for the development of the signs and symptoms of opioid withdrawal syndrome even when the patient responds appropriately to naloxone. 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.

4.9 OVERDOSAGE

There is limited clinical experience with Nyxoid overdosage in humans. Patients who experience a Nyxoid overdose should be treated symptomatically in a closely-supervised environment.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antidotes, ATC code: V03AB15

Mechanism of action

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. In the presence of physical dependence on opioids Nyxoid may produce withdrawal symptoms.

The fastest onset of action (apparent within 2 minutes) is provided by intravenous administration. Administration via subcutaneous (SC) and intramuscular route result in a slightly slower onset of action, although it was found that for SC administration, the slower onset of action was offset by not having to gain intravenous access first.

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.

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

CLINICAL TRIALS

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

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, with peak plasma concentrations being attained as early as 8 minutes (median 30 minutes) after dosing.

A study investigating intranasal naloxone at doses of 1, 2, 4 mg (MR903-1501) shows that the median t_{max} associated with intranasal administration of naloxone is between 15-30 minutes, with individuals attaining peak concentrations as early as 8 minutes. 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 IN administration were longer than for IM administration (IN, 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 IN naloxone administration.

Distribution

Distribution following administration via the nasal spray has not been studied. Following parenteral administration, naloxone is rapidly distributed in the body. It is metabolised in the liver primarily by glucuronide conjugation and the metabolites are excreted in the urine. It is 50% protein bound. The elimination half-life in adults is 60-90 minutes and 180 minutes in neonates.

Metabolism

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.

Excretion

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

Genotoxicity

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*.

Carcinogenicity

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

sodium citrate dihydrate

sodium chloride

hydrochloric acid

sodium hydroxide

purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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 nasal spray: unit dose spray device containing 0.1 mL solution. Each pack contains two single dose nasal sprays.

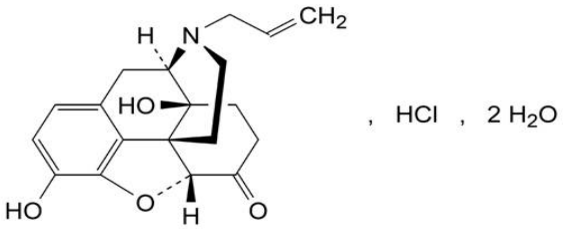
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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. 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:

Chemical structure



CAS number

51481-60-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 PHARMACIST ONLY MEDICINE

8 SPONSOR

Mundipharma Pty Limited

ABN 87 081 322 509

10 Carrington Street

SYDNEY NSW 2000

Further information may be obtained from Mundipharma's Medical Information Department 1800 188 009.

9 DATE OF FIRST APPROVAL

18-Sep-2018

10 DATE OF REVISION

4-Dec-2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

8	Update to Sponsor address ("O" - change can be made without submitting an application for TGA approval)

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