# NARCAN®

## (NALOXONE HYDROCHLORIDE) INJECTION

## 1 NAME OF THE MEDICINE

Naloxone hydrochloride dihydrate

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Narcan Injection is available as naloxone hydrochloride (as dihydrate) 400 micrograms in 1 mL of water for injections.

For the full list of excipients, see Section 6.1 List of Excipients.

## 3 PHARMACEUTICAL FORM

Narcan Injection is available as a clear colourless sterile solution for intravenous, intramuscular, and subcutaneous administration in a clear glass ampoule.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Narcan Injection is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by opioids including natural and synthetic opioids, propoxyphene, methadone and the narcotic-antagonist analgesics: nalbuphine, pentazocine and butorphanol. Narcan Injection is also indicated for the diagnosis of suspected acute opioid overdosage.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

Narcan Injection may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some opioids may exceed that of Narcan Injection the patient should be kept under continued surveillance, and repeated doses of Narcan Injection should be administered, as necessary.

Use in one patient on one occasion only and discard. Contains no antimicrobial preservative.

**Intravenous infusion**

Narcan Injection may be diluted for intravenous infusion in normal saline (sodium chloride solution) or 5% glucose solutions. The addition of 2 mg of Narcan Injection in 500 mL of either solution provides a concentration of 4 micrograms/mL. Mixtures should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Narcan Injection should not be mixed with preparations containing bisulphite, metabisulphite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to Narcan Injection unless its effect on the chemical and physical

stability of the solution has first been established.

**Usage in adults**

*Opioid overdose - known or suspected.* An initial dose of 400 micrograms to 2 mg of Narcan Injection may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of Narcan Injection have been administered, the diagnosis of opioid induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

*Postoperative opioid depression.* For the partial reversal of opioid depression following the use of opioids during surgery, smaller doses of Narcan Injection are usually sufficient. The dose of Narcan Injection should be titrated according to the patient and response. For the initial reversal of respiratory depression, Narcan Injection should be injected in increments of 100 to 200 micrograms intravenously at two to three minute intervals to the desired degree of reversal, i.e. adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of Narcan Injection may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of Narcan Injection may be required at one to two hour intervals depending upon the amount, type (i.e. short or long acting) and time since last administration of opioid. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

**Usage in children**

*Opioid overdose - known or suspected.* The usual initial dose in children is 10 micrograms/kg body weight given intravenously. If this dose does not result in the desired degree of clinical improvement a subsequent dose of 100 micrograms/kg body weight may be administered. If the intravenous route of administration is not available, Narcan Injection may be administered by intramuscular or subcutaneous injection in divided doses.

If necessary Narcan Injection can be diluted with sterile water for injections.

*Postoperative opioid depression.* Follow the recommendations and cautions under Adult Postoperative Depression. For the initial reversal of respiratory depression. Narcan Injection should be injected in increments of 5 micrograms to 10 micrograms intravenously at two to three minute intervals to the desired degree of reversal.

**Usage in neonates**

*Opioid-induced depression.* The usual initial dose is 10 micrograms/kg body weight administered by intravenous, intramuscular or subcutaneous injection. This dose may be repeated in accordance with the adult administration guidelines for postoperative opioid depression.

## 4.3 CONTRAINDICATIONS

Narcan Injection is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any other ingredients in Narcan Injection.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Narcan Injection should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

The signs and symptoms of opioid withdrawal in patients physically dependent on opioids may include, but are not limited to, the following: body aches, diarrhoea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea and vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In the neonate, opioid withdrawal may also include convulsions, excessive crying and hyperactive reflexes.

The patient who has satisfactorily responded to Narcan Injection should be kept under continued surveillance and repeated doses of Narcan Injection should be administered, as necessary, since the duration of action of some opioids may exceed that of Narcan Injection. Large doses of naloxone hydrochloride in postoperative patients may result in a clear reversal in analgesia, excitement and an elevation in blood pressure. A reversal of opioid effects achieved too rapidly may induce nausea, vomiting, sweating or tachycardia.

Narcan Injection is not effective against respiratory depression due to non-opioid drugs.

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

In addition to Narcan Injection, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute opioid poisoning.

Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary oedema and cardiac arrest which may result in death.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary oedema and cardiac arrest have been reported in post-operative patients following naloxone administration. Death, coma and encephalopathy have been reported as sequelae of these events. These have occurred in postoperative 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, Narcan Injection should be used with caution in patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation and pulmonary oedema. It has been suggested that the pathogenesis of pulmonary oedema associated with the use of Narcan Injection 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.

Narcan Injection should also be used with caution in patients with pre-existing pulmonary disease, since sudden exacerbation of underlying pulmonary disease may occur.

Each 1 mL ampoule contains 3.54 mg of sodium which corresponds to 17.7 mg of sodium per 2 mg dose (5 mL) of naloxone hydrochloride and to 3.8 mmol (88.5 mg) of sodium per maximum daily dose of 10 mg naloxone hydrochloride. This should be taken into consideration by patients on a controlled sodium diet.

**Use in hepatic impairment**

The safety and effectiveness of Narcan Injection in patients with liver disease have not been established in well-controlled clinical trials. In one small study in patients with liver cirrhosis, plasma naloxone hydrochloride

concentrations were approximately six times higher than in patients without liver disease. Caution should be exercised when Narcan Injection is administered to patients with hepatic disease.

**Use in renal impairment**

The safety and effectiveness of Narcan Injection in patients with renal insufficiency/ failure have not been established in well-controlled clinical trials. Caution should be exercised when Narcan Injection is administered to this patient population.

**Use in the elderly**

No data available.

**Paediatric use**

See Section 4.2 Dose and Method of Administration, Usage in children and Usage in neonates.

**Effects on laboratory tests**

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The effect of Narcan Injection 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 Narcan Injection dose there is no interaction with barbiturates and tranquilizers. Data on the interaction with alcohol are not uniform. In patients with multiple intoxication with opioids and sedatives or alcohol, the result of Narcan Injection administration may be delayed, dependent on the cause of intoxication.

Complete analgesia can be restored following administration of Narcan Injection 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.

Narcan Injection 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.

Narcan Injection 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 Narcan Injection 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.

No drug or chemical agent should be added to Narcan Injection unless its effect on the chemical and physical stability of the solution has first been established. Narcan Injection should not be mixed with preparations containing sulfite, metabisulfite, long chain or high molecular weight anions, or any solution having an alkaline pH.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

Reproductive studies in mice and rats demonstrated no impairment of fertility.

### Use in pregnancy

Category B1.

***Teratogenic effects***. Reproduction studies performed in mice and rats at high subcutaneous doses, revealed no evidence of impaired fertility or harm to the foetus due to Narcan Injection. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Narcan Injection should, therefore, be administered to pregnant patients only when, in the judgement of the physician, the potential benefits outweigh the possible hazards.

***Non-teratogenic effects***. Risk/ benefit must be considered before Narcan Injection is administered to a pregnant woman who is known or suspected to be opioid dependent since maternal dependence may often be accompanied by foetal dependence. Naloxone crosses the placenta and may precipitate withdrawal in the foetus as well as in the mother.

***Use in labour and delivery.*** It is not known if Narcan Injection affects the duration of labour and/or delivery.

### Use in lactation

It is not known whether Narcan Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Narcan Injection is administered to a nursing woman.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

Patients who have received naloxone hydrochloride to reverse the effect 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following undesirable effects are ranked according to system organ class and to their frequency: Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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)

<u>Immune system disorders</u>

Very rare: Allergic reactions (urticaria, rhinitis, dyspnoea, Quincke's oedema), anaphylactic shock

Nervous system disorders
Common: Dizziness, headache
Uncommon: Tremor, sweating
Rare: Seizures, tension

Seizures have occurred rarely following administration of naloxone hydrochloride; however, a causal relationship to the drug has not been established.

Cardiac disorders
Common: Tachycardia
Uncommon: Arrhythmia, bradycardia
Very rare: Fibrillation, cardiac arrest

Vascular disorders
Common: Hypotension, hypertension

Respiratory, thoracic and mediastinal disorders
Very rare: Pulmonary oedema

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting
Uncommon: Diarrhoea, dry mouth

Skin and subcutaneous tissue disorders
Very rare: Erythema multiforme
One case of erythema multiforme cleared promptly after naloxone hydrochloride was discontinued.

General disorders and administration site conditions
Common: Postoperative pain
Uncommon: Hyperventilation, irritation of vessel wall (after i.v. administration)

*Postoperative.* The following adverse events have been associated with the use of Narcan Injection in postoperative patients: hypotension, ventricular tachycardia or fibrillation, dyspnoea, pulmonary oedema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. 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.

Excessive doses of Narcan Injection in postoperative patients may result in significant reversal of analgesia and may cause agitation (see Section 4.4 Special Warnings and Precautions for Use and Section 4.2 Dose and Method of Administration, Usage in adults, Postoperative opioid depression).

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.

Higher than recommended dosage in postoperative use can lead to the return of pain. A fast reversal of opioid effect can induce hyperventilation.

*Opioid depression.* Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary oedema, and cardiac arrest which may result in death (see Section 4.4 Special Warnings and Precautions for Use).

*Opioid dependence (*see Section 4.4 Special Warnings and Precautions for Use*).* Agitation and paraesthesias have been infrequently reported with the use of Narcan Injection (naloxone hydrochloride, USP).

*Drug abuse and dependence.* Narcan Injection is an opioid antagonist.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 http://www.tga.gov.au/reporting-problems.

### 4.9 OVERDOSE

There is limited clinical experience with Narcan Injection overdosage in humans.

In a study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m$^2$/min) of Narcan Injection followed immediately by 2 mg/kg/hour for 24 hours. There were a few reports of serious adverse events: seizures (2 patients), severe hypertension (1), and hypotension and/or bradycardia (3). At doses of 2 mg/kg in normal subjects, memory impairment has been reported.

**Patient management**

Patients who experience a Narcan Injection overdose should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control centre for the most up to date patient management information.

Some chemical impurities in naloxone hydrochloride, i.e. noroxymorphone and bisnaloxone, have been shown to produce emesis in dogs when administered alone at intravenous doses equivalent to impurity levels present in naloxone at 60 times the usual human dose (10 mg/day).

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of action**

Narcan Injection, an opioid antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.

Narcan Injection prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

Narcan Injection is an essentially pure opioid antagonist, i.e. it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. Narcan Injection does not produce respiratory depression, psychotomimetic effects of pupillary constriction. In the absence of opioid or agonistic effects of other opioid antagonists it exhibits essentially no pharmacologic activity.
Narcan Injection has not been shown to produce tolerance or to cause physical or psychological dependence. In the presence of physical dependence on opioids, Narcan Injection will produce withdrawal symptoms.
While the mechanism of action of Narcan Injection is not fully understood, the preponderance of evidence suggests that Narcan Injection antagonises the opioid effects by competing for the same receptor sites.

**Clinical trials**

No data available.

### 5.2 PHARMACOKINETIC PROPERTIES

**Absorption**

When Narcan Injection is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of Narcan Injection. Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of Narcan Injection, however, will also be dependent upon the amount, type and route of administration of the opioid being antagonised.

**Distribution**

Following parenteral administration, Narcan Injection is rapidly distributed in the body.

**Metabolism**

Narcan Injection is metabolised in the liver, primarily by glucuronide conjugation.

**Excretion**

Narcan Injection is excreted in the urine. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours.

### 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

Not data available

**Carcinogenicity**

Not data available.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Narcan Injection is 400 micrograms of naloxone hydrochloride (as dihydrate) in 1 mL of water for injections. Each 1 mL of Narcan Injection contains 9.0 mg of sodium chloride. The pH is adjusted to 3.5 ± 0.5 with hydrochloric acid. Contains no antimicrobial preservative.

## 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)[1]. The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

## 6.5 NATURE AND CONTENTS OF CONTAINER

Narcan Injection is presented as a 1 mL clear glass ampoule with a red colourbreak point. It is supplied in a pack of 10 ampoules.

Phebra product code - INJ174.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

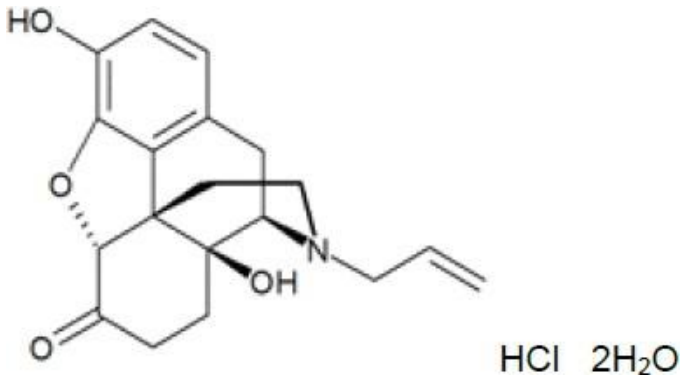
## 6.7 PHYSICOCHEMICAL PROPERTIES

Naloxone hydrochloride dihydrate occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkalis, slightly soluble in alcohol: practically insoluble in ether and in chloroform.

The molecular weight of naloxone hydrochloride dihydrate is 399.87. The molecular formula for naloxone hydrochloride dihydrate is $C_{19}H_{21}NO_4.HCl.\ 2H_2O$.

Chemical name: *(5α)*-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one hydrochloride dihydrate

**Chemical structure**




[1] AUST R 57306

**CAS number**

51481-60-8

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8 SPONSOR

Phebra[2] Pty Ltd,19 Orion Road, Lane Cove West, NSW 2066, Australia
Telephone: 1800 720 020

## 9 DATE OF FIRST APPROVAL

02 Oct 1997

## 10 DATE OF REVISION

22 Jul 2021

[2] Narcan, Phebra and the Phi symbol are registered trademarks of Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia. 

## SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| **Title** | Minor editorial changes as per current TGA's PI format. |
| **All** | Revise product name to Narcan Injection. |
| **2** | Minor editorial change from ''400 microgram'' to ''400 micrograms''. |
| **4.4** | Minor typographical correction from pilo-erection to piloerection. |
| **5.3** | Minor editorial changes as per current TGA's PI format. |
| **6.4** | Updated storage condition to 'Store below 30°C'. Minor editorial change for better readability. |
| **6.5** | Update product name and minor editorial change for better readability. |
| **9** | Minor formatting change. |