

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Naloxone Hydrochloride Injection USP 400 micrograms/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Naloxone Hydrochloride Injection USP is available in 400 micrograms/1 mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

DBL Naloxone Hydrochloride Injection USP is a sterile, clear, colourless solution, free from visible particulates. It is practically insoluble in ether or chloroform.

Naloxone hydrochloride occurs as a white to slightly off-white powder and is soluble in water, dilute acids and strong alkalis and is slightly soluble in alcohol.

The preparation has a pH of approximately 3.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Naloxone hydrochloride 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 narcotics may exceed that of naloxone hydrochloride the patient should be kept under continued surveillance and repeated doses of naloxone hydrochloride should be administered, as necessary.

Intravenous infusion Naloxone hydrochloride may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2mg of naloxone hydrochloride in 500mL of either solution provides a concentration of 0.004mg/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 discoloration prior to administration whenever solution and container permit. Naloxone hydrochloride 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 naloxone hydrochloride unless its effect on the chemical and physical stability of the solution has first been established.

Usage in Adults

Narcotic Overdose - Known or Suspected. An initial dose of 0.4mg to 2mg of naloxone hydrochloride 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 10mg of naloxone hydrochloride have been administered, the diagnosis of narcotic induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Narcotic Depression. For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of naloxone hydrochloride are usually sufficient. The dose of naloxone hydrochloride should be titrated according to the patient and response. For the initial reversal of respiratory depression, naloxone hydrochloride should be injected in increments of 0.1 to 0.2mg intravenously at two to three minute intervals to the desired degree of reversal i.e. adequate ventilation and alertness without significant pain or discomfort.

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

Usage in Children

Narcotic Overdose - Known or Suspected. The usual initial dose in children is 0.01mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement a subsequent dose of 0.1mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone hydrochloride may be administered I.M. or S.C. in divided doses if necessary. naloxone hydrochloride can be diluted with sterile. Water for Injection.

Postoperative Narcotic Depression. Follow the recommendations and cautions under Adult Postoperative Depression. For the initial reversal of respiratory depression naloxone hydrochloride should be injected in increments of 0.005mg to 0.01mg intravenously at two to three minute intervals to the desired degree of reversal.

Usage in Neonates

Narcotic-induced Depression. The usual initial dose is 0.01mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative narcotic depression.

4.3 Contraindications

Naloxone hydrochloride is contraindicated in patients with hypersensitivity to naloxone or to any of the excipients.

4.4 Special warnings and precautions for use

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

The patient who has satisfactorily responded to naloxone hydrochloride should be kept under continued surveillance and repeated doses of naloxone hydrochloride should be administered, as necessary, since the duration of action of some narcotics may exceed that of naloxone hydrochloride.

Naloxone hydrochloride is not effective against respiratory depression due to non-opioid drugs. Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete or require higher doses of naloxone. If an incomplete response occurs, respirations should be mechanically assisted as clinically indicated. In addition to naloxone hydrochloride, 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 narcotic poisoning.

Several instances of hypotension, hypertension, ventricular tachycardia and atrial fibrillation, pulmonary oedema and cardiac arrest have been reported. 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, naloxone hydrochloride should be used with caution in patients with pre-existing cardiac disease or patients who have received potentially cardiotoxic drugs.

Excessive doses of naloxone following the use of opioids in surgery should be avoided because it may result in agitation, increased blood pressure and clinically important reversal of analgesia. Too rapid reversal of opioid effects may induce nausea, vomiting, sweating, tachycardia, tremors or hyperventilation.

Paediatric use

Naloxone should be given with caution to patients who are known or suspected to be physically dependent on opioids (including neonates born to women who are opioid dependent), because the drug may precipitate the onset of severe withdrawal symptoms.

4.5 Interaction with other medicines and other forms of interaction

Large doses of naloxone are required to antagonize buprenorphine since the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor. Buprenorphine antagonism is characterized by a gradual onset of the

reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

Naloxone reverses the analgesic and other effects of opioid agonist-antagonists such as pentazocine, so may precipitate withdrawal symptoms if used concurrently with these drugs 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 drugs in physically dependent patients, including patients receiving methadone to treat opioid dependence.

When naloxone is used post-operatively 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 post-operative pain, or causing other adverse effects.

4.6 Fertility, pregnancy and lactation

Fertility

Reproduction studies performed in mice and rats at doses up to 1,000 times the human dose, revealed no evidence of impaired fertility or harm to the foetus due to naloxone hydrochloride.

Pregnancy

There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should, therefore, be administered to pregnant patients only when, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Lactation

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

4.7 Effects on ability to drive and use machinery

DBL Naloxone Hydrochloride Injection USP may be likely to produce minor or moderate adverse effects that may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines.

4.8 Undesirable effects

The adverse effects are listed within each system organ class (SOC).

Table 1. Adverse Drug Reaction Table	
System Organ Class	Adverse Drug Reactions
Psychiatric disorders	Agitation
Nervous system disorders	Convulsions, tremors

Table 1. Adverse Drug Reaction Table	
System Organ Class	Adverse Drug Reactions
Cardiac disorders	Cardiac arrest, atrial fibrillation, ventricular tachycardia, tachycardia
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema, hyperventilation
Gastrointestinal disorders	Vomiting, nausea
Skin and subcutaneous tissue disorders	Sweating

Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, larger than necessary dosage of naloxone hydrochloride may result in significant reversal of analgesia, and in excitement. Hypotension, ventricular tachycardia and fibrillation, and pulmonary oedema have been associated with the use of naloxone hydrochloride postoperatively (see section 4.4 and section 4.2). Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

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

There is no clinical experience with naloxone hydrochloride overdosage in humans. In the mouse and rat the intravenous LD₅₀ is 150 ± 5mg/kg and 109 ± 4mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD₅₀ (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injection, no toxic effects were seen at 10mg/kg/day for 3 weeks.

Symptoms

Symptoms of overdosage would be expected to be similar to the effects seen with therapeutic use (see section 4.8).

Treatment

Treatment of overdosage is symptomatic and supportive.

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

Mechanism of action

Naloxone hydrochloride, a narcotic antagonist, is a synthetic congener of oxymorphone. Naloxone hydrochloride 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. Naloxone hydrochloride is an essentially pure narcotic antagonist, i.e. it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; Naloxone hydrochloride does not produce respiratory depression, psychotomimetic effects of pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

Naloxone hydrochloride has not been shown to produce tolerance nor to cause physical or psychological dependence. In the presence of physical dependence on narcotics naloxone hydrochloride will produce withdrawal symptoms.

While the mechanism of action of naloxone hydrochloride is not fully understood, the preponderance of evidence suggests that naloxone hydrochloride antagonises the opioid effects by competing for the same receptor sites.

5.2 Pharmacokinetic properties

When naloxone hydrochloride 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 naloxone hydrochloride. Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of naloxone hydrochloride, however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonised.

Following parenteral administration naloxone hydrochloride is rapidly distributed in the body. It is metabolised in the liver, primarily by glucuronide conjugation and 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/Carcinogenicity

Carcinogenicity and mutagenicity studies have not been performed with naloxone hydrochloride.

Reproductive and developmental toxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hydrochloric acid
- Sodium chloride
- Water for injection

6.2 Incompatibilities

Naloxone hydrochloride solution for injection should not be mixed with preparations containing bisulfites, metabisulfites, long chain or high molecular weight anions, or those with an alkaline pH.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Protect from light. Store below 25°C.

6.5 Nature and contents of container

DBL Naloxone Hydrochloride Injection USP is available in ampoules in the following strength:

400 micrograms naloxone hydrochloride/1 mL

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited

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Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

01 Oct 1992

10. DATE OF REVISION OF THE TEXT

8 October 2020

Summary table of changes

Section changed	Summary of new information
4.3	- Inclusion of contraindication to other excipients of DBL Naloxone Injection.
4.4	<ul style="list-style-type: none">- Added pentazocine and buprenorphine incomplete reversal of respiratory depression.- Updated fibrillation to atrial fibrillation.- Added potential cardiovascular effect cardiac arrest for medications interacting with naloxone.- Added hyperventilation as result of abrupt post-operative reversal of opioid depression- Updated Paediatric use of Naloxone.
4.5	- Added interaction with buprenorphine
4.8	- Added a summarised table of adverse events based on sytem organ class (SOC)
6.2	- Added incompatibilities to naloxone