AUSTRALIAN PRODUCT INFORMATION – DBL™ NALOXONE HYDROCHLORIDE INJECTION (Naloxone hydrochloride dihydrate)

1. NAME OF THE MEDICINE

Naloxone hydrochloride dihydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Naloxone Hydrochloride contains 400 micrograms/1 mL naloxone hydrochloride dihydrate and sodium chloride in water for injections. The preparation has a pH of approximately 3.5.

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

3. PHARMACEUTICAL FORM

DBL Naloxone Hydrochloride Injection is a sterile, clear, colourless solution, free from visible particulates.

Naloxone is a semi-synthetic opioid antagonist which differs structurally from oxymorphone only in that the methyl group on the nitrogen atom of oxymorphone is replaced by an allyl group.

Naloxone hydrochloride dihydrate is 17-allyl-4,5 α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride.

Naloxone hydrochloride dihydrate 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. It is practically insoluble in ether or chloroform.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Naloxone is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids including propoxyphene, methadone, codeine, morphine and heroin, and the mixed opioid agonist-antagonist analgesics such as pentazocine. Naloxone is also indicated for the diagnosis of suspected acute opioid overdosage.

4.2 Dose and Method of Administration

Dosage

Use in adults

Opioid overdosage – known or suspected: An initial dose of 400 micrograms (0.4 milligrams) to 2 milligrams of naloxone hydrochloride may be administered intravenously. This dose may be repeated at 2 to 3 minute intervals, if necessary. If no response is seen after a total of 10 milligrams has been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. If the intravenous route is not available, the medicine may be administered by intramuscular or subcutaneous injection.

Post-operative opioid depression: For the partial reversal of opioid-induced depression following the use of opioids during surgery, smaller doses of naloxone are usually sufficient. The dose should be titrated according to the patient's response. The usual initial dosage is 100 to 200 micrograms (0.1 to 0.2 milligrams) administered intravenously at 2 to 3 minute intervals until the desired degree of reversal is achieved, i.e. adequate ventilation and alertness without significant pain or discomfort. Doses of naloxone larger than necessary may result in significant reversal of analgesia and increase in blood pressure. Too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of naloxone may be required within one or two hours, depending on the type and amount of opioid administered and the time interval since the last dose. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

Use in children

Opioid overdose - known or suspected: The usual initial dose in children is 10 micrograms (0.01 milligrams) per kg body weight given intravenously. If the desired degree of clinical improvement is not seen, a subsequent dose of 100 micrograms (0.1 milligrams) per kg may be administered. If the intravenous route is not available, naloxone may be administered by intramuscular or subcutaneous injection in divided doses. If necessary, naloxone can be diluted with sterile water for injections.

Post-operative opioid depression: Follow the recommendations and cautions under "Adult post-operative opioid depression". In children the initial dose of naloxone hydrochloride for reversal of respiratory depression should be in increments of 5 to 10 micrograms (0.005 to 0.01 milligrams) administered intravenously at 2 to 3 minute intervals until the desired degree of reversal is achieved.

Use in neonates

Opioid-induced depression: The usual initial dose is 10 micrograms (0.01 milligrams) per kg body weight administered by intravenous, intramuscular or subcutaneous injection. This dose may be repeated in accordance with the adult administration guidelines for post-operative opioid depression.

Method of Administration

DBL Naloxone Hydrochloride Injection may be administered by the intravenous, intramuscular or subcutaneous route. Intravenous administration is recommended in emergency situations, as this route of administration provides the most rapid onset of action.

The duration of action of naloxone may be shorter than that of some opioids. Therefore, the patient should be kept under continued surveillance and repeated doses of naloxone should be administered as necessary.

Continuous intravenous infusion of DBL Naloxone Hydrochloride Injection may be the most appropriate method of administration for patients who require higher doses, or who continue to experience respiratory or central nervous system (CNS) depression after effective therapy with repeated doses, and/or in whom the effects of long acting opioids are being antagonised. For continuous intravenous infusion, 2 milligrams of naloxone hydrochloride may be diluted in 500 mL of sodium chloride 0.9% or glucose 5% injection to produce a solution containing 4 micrograms/mL.

DBL Naloxone Hydrochloride Injection should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions or any solution having an alkaline pH. No medicine or chemical agent should be added to naloxone unless its effect on the chemical and physical stability has first been established. Prior to administration, intravenous solutions of DBL Naloxone Hydrochloride Injection should be visually inspected for the presence of particles or discolouration. Diluted solutions of the medicine should be used within 24 hours of preparation and any unused portion discarded after this time.

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

Naloxone should be administered with caution to patients who have received large doses of opioids, or 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 severe withdrawal symptoms.

The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include, but are not limited to, the following: body aches, diarrhoea, tachycardia, fever, runny nose, sneezing, pilo-erection, sweating, yawning, nausea or 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.

Patients who have satisfactorily responded to naloxone should be carefully monitored since the duration of action of some opioids may exceed that of naloxone. Repeated doses of naloxone should be administered when necessary.

Naloxone is not effective against respiratory depression caused by 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 (see also section 4.2 Dose and method of administration). If an incomplete response occurs, respirations should be mechanically assisted as clinically indicated.

When naloxone is used in the management of acute opioid overdosage, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage and vasopressor agents should be readily available and used when necessary.

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. Although a direct cause and effect relationship has not been established, naloxone should be used with caution in patients with pre-existing cardiac disease or patients who have received potentially cardiotoxic drugs, since serious cardiovascular effects, such as hypotension, hypertension, ventricular tachycardia or fibrillation, pulmonary oedema and cardiac arrest have occurred. It has been suggested that the pathogenesis of pulmonary oedema associated with the use of naloxone 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.

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

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

Use in hepatic impairment

The safety and effectiveness of naloxone in patients with hepatic disease have not been established in well controlled clinical trials. In one small study in patients with hepatic cirrhosis, plasma naloxone concentrations were approximately six times higher than in patients without hepatic disease. Caution should be exercised when naloxone is administered to patients with hepatic disease.

Use in renal impairment

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

Use in the elderly

No data available.

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.

Effects on laboratory tests

None known.

4.5 Interactions with Other Medicines and Other Forms of Interactions

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.

High doses of naloxone may be 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 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 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

Effects on fertility

No evidence for impaired fertility was observed in a reproductive study in male or female rats given naloxone at doses 8 times the highest recommended human dose (based on body surface area).

Use in pregnancy – Category B1

Category B1: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus being observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.*

There are no adequate and controlled studies of naloxone in pregnant women. Naloxone should be administered to a pregnant woman only when, in the judgement of the physician, the potential benefits outweigh the possible hazards. Caution should be used when administering naloxone to a pregnant woman who is known 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.

Reproduction studies in mice and rats at doses of 4 to 8 times the highest recommended human dose (based on body surface area) revealed no evidence of harm to the foetus.Use in lactation

It is not known whether naloxone is excreted in human milk. Therefore, naloxone should be used with caution in breastfeeding women.

4.7 Effects on Ability to Drive and Use Machines

The effect of naloxone on the ability to drive or use machines has not been systematically evaluated.

4.8 Adverse Effects (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
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

Post-operative

The following adverse events have been associated with the use of naloxone in post-operative patients: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnoea, pulmonary oedema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone 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 Dosage and Method of Administraton).

Opioid depression

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, hyperventilation, 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)

Naloxone may precipitate severe withdrawal symptoms in patients known or suspected to be physically dependent on opioids (including neonates born to women who are opioid dependent) (see Section 4.4 Special Warnings and Precautions for Use). Agitation and paraesthesias have been infrequently reported with the use of Naloxone. Seizures have occurred rarely following administration of naloxone, however, a causal relationship has not been established. Violent behaviour, nervousness, restlessness, excitement and irritability may also occur.

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 www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms

Symptoms of overdosage would be expected to be similar to the effects seen with therapeutic use (see Section 4.8 Adverse Effects(Undesirable Effects).

Treatment

Treatment of overdosage is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Naloxone is essentially a pure opioid antagonist, it has little or no agonistic activity. Naloxone is thought to act as a competitive antagonist at mu, kappa, and sigma opioid receptors in the central nervous system (CNS), although the precise mechanism of action has not been fully determined. Naloxone prevents or reverses the effects of opioids, including respiratory depression, sedation and hypotension. Naloxone can also reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine, but higher doses are required. One milligram of naloxone intravenously completely blocks the effects of 25 milligrams of diacetylmorphine (heroin).

When administered in usual doses to patients who have not recently received opioids, naloxone exerts little or no pharmacological effect. Even extremely high doses (10 times the usual therapeutic dose) produce insignificant analgesia, only slight drowsiness, and no respiratory depression, psychotomimetic effects, circulatory changes or miosis.

Naloxone does not produce tolerance or physical or psychological dependence.

Parenteral administration of naloxone will produce withdrawal symptoms in patients physically dependent on opioids or pentazocine.

Clinical trials

No data available.

5.2 Pharmacokinetic Properties

Absorption

Naloxone has an onset of action within 1 to 2 minutes following intravenous administration and within 2 to 5 minutes following subcutaneous or intramuscular administration. The duration of action depends on the dose and route of administration and is more prolonged following intramuscular administration than after intravenous administration. The duration of action is reported to be up to several hours but the practical duration is probably 1 hour or less. Repeat doses of naloxone may be required depending on the amount, type and route of administration of the opioid being antagonised, as well as the duration of action of naloxone.

Distribution

Following parenteral administration, naloxone is rapidly distributed into body tissues and fluids.

Metabolism

Naloxone is rapidly metabolised in the liver, principally by conjugation with glucuronic acid.

Excretion

Naloxone is 50% protein-bound and is excreted in the urine. The mean plasma half-life of naloxone has been reported to be about 60 minutes in adults with a range of from about 30 to 80 minutes, and about 3 hours in neonates.

5.3 Preclinical Safety Data

Genotoxicity

In assays for gene mutations, naloxone was positive in the Ames test but negative in the mouse lymphoma assay. Naloxone was also positive in an assay for chromosomal damage (human lymphocytes *in vitro*).

Carcinogenicity

Studies in animals to assess the carcinogenic potential of naloxone have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Hydrochloric acid
Sodium Chloride
Water for Injections

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

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

Protect from light. Store below 25°C.

6.5 Nature and Contents of Container

DBL Naloxone Hydrochloride Injection is available in ampoules:

400 micrograms naloxone hydrochloride/1 mL

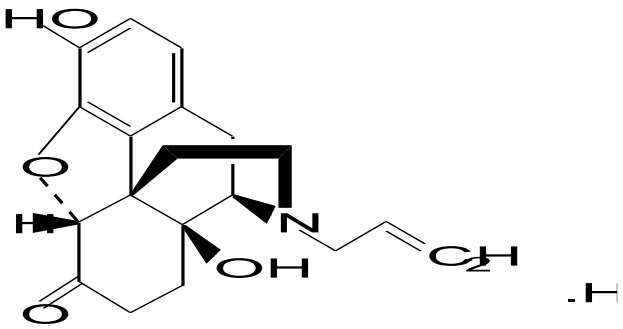
6.6 Special Precautions for Disposal

Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Chemical structure

Its chemical structure is shown below:



The chemical formula for anhydrous naloxone hydrochloride is $C_{19}H_{21}NO_4.HCl$. Its molecular weight is 363.84

CAS number

CAS registry number is 357-08-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number : 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

8 October 1991

10. DATE OF REVISION

27 November 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	- Added pentazocine and buprenorphine incomplete reversal of respiratory depression. - Added potential cardiovascular effects - hypertension and 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
4.7	- Update to information regarding driving and using machines.
4.8	- Added a summarised table of adverse events based on system organ class (SOC).
6.2	- Added incompatibilities to naloxone