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# DBL™ NALOXONE HYDROCHLORIDE INJECTION USP

## Name of medicine

Naloxone hydrochloride

## Presentation

DBL™ Naloxone Hydrochloride Injection USP is a sterile, clear, colourless solution, free from visible particulates. It is available in 400 micrograms/1 mL containing sodium chloride in water for injections. The preparation has a pH of approximately 3.5.

## Uses

### Actions

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.

### Pharmacokinetics

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  $64 \pm 12$  minutes). In a neonatal study the mean plasma half-life was observed to be  $3.1 \pm 0.5$  hours.

### 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.

### Dosage and 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. Larger than necessary dosage of naloxone hydrochloride 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 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.

## **Contraindications**

Naloxone hydrochloride is contraindicated in patients known to be hypersensitive to it.

## **Warnings and precautions**

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. 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 fibrillation, and pulmonary oedema 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.

### ***Pregnancy and Lactation***

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. 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.

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.

### ***Effects on ability to drive and use machines***

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.

### ***Other***

#### *Carcinogenesis, Mutagenesis, Impairment of Fertility*

Carcinogenicity and mutagenicity studies have not been performed with naloxone hydrochloride. Reproductive studies in mice and rats demonstrated no impairment of fertility.

### ***Adverse effects***

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 Warnings and Precautions & Usage in Adults Postoperative Narcotic Depression). Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

### ***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 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.

## Overdosage

There is no clinical experience with naloxone hydrochloride overdosage in humans. In the mouse and rat the intravenous LD<sub>50</sub> is 150 ± 5mg/kg and 109 ± 4mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD<sub>50</sub> (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 **ADVERSE REACTIONS**).

## Treatment

Treatment of overdosage is symptomatic and supportive.

## Pharmaceutical precautions

### *Special Precautions for Storage*

Protect from light. Store below 25°C.

## Medicine classification

Prescription Medicine.

## Package quantities

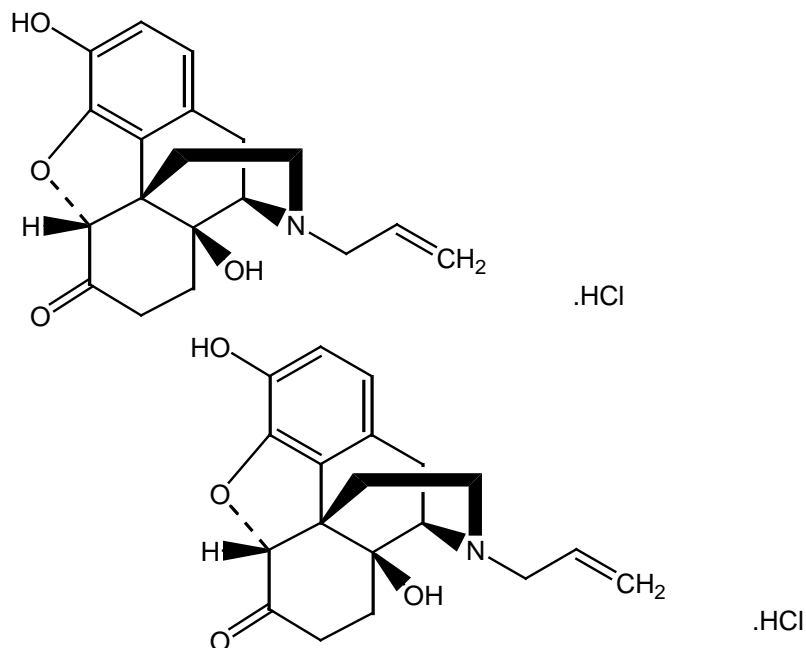
DBL™ Naloxone Hydrochloride Injection USP is available in ampoules in the following strength:

400 micrograms naloxone hydrochloride/1 mL

## Further information

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 is 17-allyl-4,5 α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. Its chemical structure is shown below:



The chemical formula for anhydrous naloxone hydrochloride is C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub>.HCl. Its molecular weight is 363.84 and its CAS registry number is 357-08-4.

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. It is practically insoluble in ether or chloroform.

**Name and address**

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