PRODUCT MONOGRAPH

PrNALOXONE HYDROCHLORIDE INJECTION USP

Naloxone Hydrochloride

0.4 mg/mL

Opioid Antagonist

Hikma Canada Limited
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Date of Preparation:
May 13, 2022

Control No.: 263217

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Therapeutic Classification

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CLINICAL PHARMACOLOGY

Naloxone hydrochloride prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension. Also, it can reverse the psychosomimetic and dysphonic effects of agonist-antagonists such as pentazocine. Naloxone hydrochloride is an essentially pure opioid antagonist, i.e., it does not possess the agonistic or morphine like properties characteristic of other opioid antagonists; naloxone does not produce respiratory depression, psychosomimetic effects or pupillary constriction. 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 to cause physical or psychological dependence. In the presence of physical dependence on opioids naloxone will produce withdrawal symptoms.

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

Following parenteral administration naloxone is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in urine.

INDICATIONS AND CLINICAL USE

Naloxone 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 agonist-antagonist analgesics nalbuphine, pentazocine and butorphanol. Naloxone is also indicated for the diagnosis of suspected acute opioid overdosage.

Naloxone is not effective in counteracting depression due to barbiturates, tranquillizers or

other non-opioid anesthetics or sedatives. It has been safely administered to patients who received both opioid and non-opioid drugs.

CONTRAINDICATION

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

WARNINGS

Naloxone should be administered cautiously to persons, including newborns of dependent 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 abstinence syndrome. The severity of such a syndrome will depend on the degree of physical dependence and the dose of antagonist administered. In the presence of serious respiratory depression in a physically dependent individual, the antagonist, when indicated, should be administered with extreme care, under close monitoring, by using appropriate titration with smaller doses than usual.

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

Naloxone is not effective against respiratory depression due to non-opioid drugs (see **INDICATIONS AND CLINICAL USE**). It has been safely administered to patients who received both opioid and non-opioid drugs. Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs, respiration should be mechanically assisted.

Use in Pregnancy

Reproduction studies performed in mice and rats at doses up to 1000 times the human dose revealed no evidence of impaired fertility or harm to the fetus due to naloxone. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone should be used during pregnancy only if clearly needed.

Nursing Mothers

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

PRECAUTIONS

In addition to naloxone 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.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. These have occurred in postoperative patients in whom preexisting cardiovascular disorders or other drugs may have contributed to the adverse cardiovascular effects.

Although a direct cause-and-effect relationship has not been established, naloxone should be used with caution in patients with preexisting cardiac disease or patients who have received potentially cardiotoxic drugs. The clinical course should be monitored by ECG.

ADVERSE REACTIONS

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, larger than necessary dosages of naloxone may result in significant reversal of analgesia and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation and pulmonary edema have been associated with the use of naloxone postoperatively (see **PRECAUTIONS** and **USAGE IN ADULTS - Postoperative Opioid Depression**). Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no clinical experience with naloxone overdosage in humans.

For management of a suspected drug overdose, contact your regional Poison Control Centre

DOSAGE AND ADMINISTRATION

Naloxone hydrochloride may be administered intravenously (IV), intramuscularly (IM), or subcutaneously (SC). 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 naloxone, the patient should be kept under continued surveillance and repeated doses of naloxone should be administered, as necessary.

Intravenous Infusion

Infusion may be useful in cases of overdose with long acting drugs such as methadone and propoxyphene. The infusion rate for adults is approximately 100 mL/hour (0.4 mg/hour). Infusion rate and concentration should be individually adjusted to obtain the desired antagonist effect without fluid overload or production of withdrawal.

Dilution for Intravenous Use

Naloxone may be diluted for intravenous infusion in 0.9% Sodium Chloride Injection or 5% Dextrose Injection. The addition of 2 mg of Naloxone Hydrochloride Injection USP in 500 mL of diluent provides a concentration of 4 mcg (0.004 mg)/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. Naloxone 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 unless its effect on the chemical and physical stability of the solution has first been established.

USAGE IN ADULTS

Opioid Overdosage - Known or Suspected

An initial dose of 0.4 mg to 2 mg of naloxone may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at two to three-minute intervals. If no response is observed after 10 mg of naloxone has been administered, the diagnosis of opioid-induced or partial opioid 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 naloxone are usually sufficient. The dose of naloxone should be titrated according to the patient's response. Naloxone should be injected in increments of 0.1 to 0.2 mg 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 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 may be required within one to two-hour intervals depending upon the amount, type (i.e., short or long-acting) and time interval since last administration of opioid. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN

Opioid Overdosage - Known or Suspected

The usual initial dose in children is 0.01 mg/kg body weight given IV. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an IV route of administration is not available, naloxone may be administered IM or SC in divided doses. If necessary, naloxone can be diluted with sterile water for injection.

Postoperative Opioid Depression

Follow the recommendations and cautions under "**Adults Postoperative Opioid Depression**". For the initial reversal of respiratory depression naloxone should be injected in increments of 0.005 mg to 0.01 mg intravenously at two to three-minute intervals to, the desired degree of reversal.

USAGE IN NEONATES

Opioid-Induced Depression

The usual dose is 10 mcg (0.01 mg)/kg body weight administered IV, IM or SC routes. This dose may be repeated in accordance with audit administration guidelines.

SUMMARY OF DOSAGES:	
Adults	**Opioid Overdose** 0.4 to 2 mg IV repeated if necessary at 2 to 3- minute intervals. **Postoperative Opioid Depression** 0.1 to 0.2 mg IV repeated if necessary at 2 to 3-minute intervals. IV, IM or SC.
Children	**Opioid Overdose** 0.01 mg/kg IV. If desired degree of improvement is not obtained, 0.1 mg/kg IV may be administered. Naloxone may be diluted with sterile water for injection. **Postoperative Opioid Depression** 0.005 to 0.01 mg IV repeated if necessary at 2 to 3-minute intervals.
Neonates	**Opioid-Induced Depression** 0.01 mg/kg IV, IM or SC repeated if necessary at 2 to 3-minute intervals. Naloxone may be diluted with sterile water for injection.

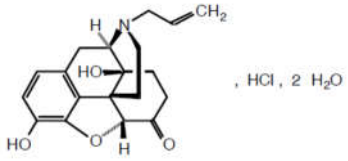
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Common Name: Naloxone hydrochloride dihydrate

Chemical Name: 4,5α-Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dehydrate

Structural Formula:



Molecular Formula: $C_{19}H_{21}NO_4$, HCl, $2H_2O$

Molecular Weight: 399.9 g/mol

Description: Naloxone hydrochloride, 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.

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform. It melts at about 200-205°C. The pH of aqueous solutions is acidic.

COMPOSITION

Naloxone Hydrochloride Injection USP, 0.4 mg/mL: Each mL of aqueous injectable solution contains: naloxone hydrochloride 400 mcg (as naloxone hydrochloride dihydrate), sodium chloride, hydrochloric acid to adjust pH, and water for injection.

STABILITY AND STORAGE RECOMMENDATIONS

Naloxone Hydrochloride Injection USP should be stored at 25°C, with excursions permitted to 15°C - 30°C, protected from light. Do not remove the ampoule from the carton until prior to use. Following dilution with 5% Glucose or 0.9% Sodium Chloride, Naloxone Hydrochloride Injection USP can be stored up to 24 hours at room temperature.

AVAILABILITY OF DOSAGE FORMS

Naloxone Hydrochloride Injection USP is available in 0.4 mg/mL, 1 mL ampoules, boxes of 10 **(discard unused portion).**

PHARMACOLOGY

Single subcutaneous doses of naloxone as high as 24 mg/70 kg (0.343 mg/kg) and multiple doses of 90 mg daily, for two weeks, administered to normal volunteers produced no behavioural or physiological changes, yet its antagonistic activity to subsequent morphine challenge persisted.

Naloxone hydrochloride at doses of 0.7 to 10 mg administered intravenously to heroin addicts abolished the effects of l0 to 20 mg of heroin whether administered before or after the heroin. The effects of the heroin began to recur three hours after naloxone administration, indicating naloxone has a shorter duration of action than heroin.

Naloxone was able to reverse the respiratory depression induced by various anesthetics: morphine, fentanyl, cyc1azocine, pentazocine, meperidine, alphaprodine, oxymorphone, nalorphine and levallorphan in patients, whether administered IV, IM or SC at 0.4 to 2 mg/mL. Naloxone caused no respiratory depression, psychotomimetic effects, clinically significant circulatory effects, nor analgesia when administered alone. Subjects did not develop tolerance to naloxone. Temporary nausea and vomiting were reported in two studies, but as other anesthetics/analgesics were being administered concurrently, these effects could not be causally related to naloxone.

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

Following parenteral administration naloxone is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in urine. In one study the mean serum half-life in adults was 4.7 minutes for the distribution phase and 64 minutes for the elimination phase. In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours.

In a nine-week study of nine males (22 to 47 years of age) who were addicted to opioids, naloxone was administered in single daily oral doses in increments of 50 mg (3 subjects), 100 mg (4 subjects) and 300 mg (2 subjects). Up to 3000 mg of naloxone hydrochloride daily was administered (1 subject). No significant toxic symptoms occurred over nine weeks of naloxone administration. Sporadic abnormal laboratory findings including elevated white blood cell counts occurred, but are common in cases of opioid addiction.

One patient receiving 1500 mg of naloxone daily reported psychic depression, apathy and decreased appetite, which were relieved when the dosage was decreased.

TOXICOLOGY

Acute Toxicity

The maximum non-toxic subcutaneous dose in rats was 50 mg/kg.

In acute SC toxicity studies in newborn rats, the LD_{50} is 260 mg/kg. Naloxone was only twice as toxic in newborn as in six week-old rats. At toxic doses naloxone produced excitation, hyperactivity, salivation, tremors, and tonic-clonic convulsions. Respiration was slightly stimulated in rabbits as shown by the minute-volume measurements.

Subacute Toxicity

Subacute SC toxicity experiments in rats and monkeys and a subacute IV toxicity experiment in dogs demonstrated very little cumulative toxicity and no organic pathological changes.

Reproduction and Teratology

Reproduction studies in mice and rats using naloxone hydrochloride dosages up to 1000 times the usual human dosage have not revealed evidence of impaired fertility or harm to the fetus.

Mutagenicity and Carcinogenicity

Mutagenicity and carcinogenicity studies have not been conducted using naloxone.

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Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/healthcanada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more Information about NALOXONE HYDROCHLORIDE INJECTION USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-800-656-0793.

This leaflet was prepared by
Hikma Canada Limited
Mississauga, Ontario
L5R 3P9

Last revised: May 13, 2022