PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

INJECTABLE NALOXONE HYDROCHLORIDE

Naloxone Hydrochloride Injection

Naloxone Hydrochloride (as dihydrate)

0.4 mg / mL and 1 mg / mL Sterile Solution

Omega Standard

Opioid Antagonist

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous, subcutaneous, intramuscular	Aqueous Solution, 0.4 mg / mL and 1 mg / mL	Hydrochloric acid, methylparaben, propylparaben, sodium chloride, and water for injection

INDICATIONS AND CLINICAL USE

INJECTABLE NALOXONE HYDROCHLORIDE (naloxone hydrochloride) is a pure opioid antagonist indicated for emergency use to reverse known or suspected opioid overdoses, as manifested by respiratory depression and/or severe central nervous system depression.

INJECTABLE NALOXONE HYDROCHLORIDE can be administered by a bystander (non-health care professional) before emergency medical assistance becomes available but it is not intended to be a substitute for professional medical care. Emergency medical assistance (calling 911) should be requested immediately when an opioid overdose is suspected, before injecting naloxone**.**

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Emergency medical assistance (calling 911) should be requested immediately when an opioid overdose is suspected, before injecting naloxone (see WARNINGS AND PRECAUTIONS, Rebound Opioid Toxicity).

- Individuals with a satisfactory response to an initial dose of INJECTABLE NALOXONE HYDROCHLORIDE should be kept under continued surveillance (see WARNINGS AND PRECAUTIONS, Rebound Opioid Toxicity); repeated doses of INJECTABLE NALOXONE HYDROCHLORIDE should be administered as needed until the emergency medical services become available (see DOSAGE AND ADMINISTRATION).

- Caregivers administering INJECTABLE NALOXONE HYDROCHLORIDE should be prepared to assist the patient for potential adverse reactions such as aggressive reactions, convulsions and vomiting. Special attention is warranted if INJECTABLE NALOXONE HYDROCHLORIDE is administered to a neonate (see WARNINGS AND PRECAUTIONS, Acute Opioid Withdrawal Syndrome and *Special Populations,* Pediatrics).

General

In the absence of opioids, in opioid naïve people, naloxone shows essentially no pharmacologic activity. In opioid tolerant people, naloxone may trigger an acute opioid withdrawal syndrome (see WARNINGS AND PRECAUTIONS, Acute Opioid Withdrawal Syndrome).

INJECTABLE NALOXONE HYDROCHLORIDE does not counteract overdoses due to: barbiturates, benzodiazepines, psychostimulants (*e.g.* cocaine, amphetamines, methylphenidate, etc.), alcohol, or any other non-opioid drug such as non-opioid tranquilizers, anesthetics or sedatives. However, mistakenly administering naloxone to a person that is unconscious because of a non-opioid overdose or for other reasons is unlikely to create more harm.

Rebound Opioid Toxicity

Rebound opioid toxicity is the re-emergence of an opioid overdose manifestation, including respiratory depression, following the temporary reversal of the opioid overdose with naloxone. The patient who has responded satisfactorily to naloxone should be kept under continued surveillance and repeated doses of naloxone should be administered as necessary until the emergency medical services take charge of the patient (see DOSAGE AND ADMINISTRATION). Repeated doses are often required as the duration of action of most opioids exceeds that of naloxone, and therefore, re-emergence of opioid overdose manifestation is likely.

Respiratory
Naloxone is not effective against respiratory depression due to non-opioid drugs (see WARNINGS AND PRECAUTIONS, General). A single dose of naloxone may not reverse respiratory depression (or reversal may be incomplete) if the opioid overdose is caused by certain partial agonist opioids such as buprenorphine and pentazocine or highly potent opioids such as fentanyl. Additional doses of naloxone administered at close intervals may be required in such cases (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment). Similarly, an opioid overdose caused by very large dose of any opioid may also require administration of multiple doses of naloxone at close intervals (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment). In addition to naloxone, other resuscitative measures such as maintenance of a free airway, artificial ventilation and cardiac massage could be executed by a bystander (non-health care professionals) if the bystander knows how to perform the manoeuvers. Moreover, vasopressor agents should be employed (if available) whenever necessary if a health care professional is present.

Acute Opioid Withdrawal Syndrome
INJECTABLE NALOXONE HYDROCHLORIDE should be administered with caution to persons 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 opioid withdrawal syndrome. The severity of such a syndrome will depend on the degree of physical dependence, the dose, affinity and potency of the opioid that induced the overdose, and the dose of naloxone administered.

The signs and symptoms of an acute opioid withdrawal syndrome include, but are not limited to: body aches, pain, fever/pyrexia, sweating/hyperhidrosis, runny nose, sneezing, piloerection, yawning, weakness, asthenia, shivering, chills, tremor/trembling, convulsions/seizures, nervousness, restlessness, irritability, aggressive behavior, diarrhea, nausea, vomiting, abdominal cramps, increased blood pressure and tachycardia. In the dependent neonate, signs also include excessive crying as well as hyperactive reflexes and the acute withdrawal may be life threatening if not recognized and properly treated (see WARNINGS AND PRECAUTIONS, *Special Populations*, Pediatrics).

Caregivers administering INJECTABLE NALOXONE HYDROCHLORIDE to any patient should always be prepared for potential reactions associated with acute opioid withdrawal syndrome and to assist the patient to minimize harm when experiencing these reactions. For example, a patient should be positioned in lateral decubitus to prevent choking if vomiting occurs; sharp or dangerous objects should be moved away in case of seizures to protect the patient from injury, but the patient should not be restrained.

Cardiovascular - Post-Operative
Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. Rare cases of cardiac arrest have also been reported. These have occurred in postoperative patients with pre-existing cardiovascular disorders and/or

other drugs may have contributed to the adverse events. A direct relationship to naloxone has not been established.

Neurologic
Convulsions or seizures after naloxone administration have been rarely reported and the relationship between naloxone and convulsion or seizure is unclear. If convulsions or seizures occur, sharp or dangerous objects should be moved away to protect the patient from injury but the patient should not be restrained.

Special Populations
Pregnant Women: There are, no adequate and well-controlled studies in pregnant women. Although 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, administration of INJECTABLE NALOXONE HYDROCHLORIDE to an opioid-dependent pregnant woman may induce an acute opioid withdrawal syndrome (see WARNINGS AND PRECAUTIONS, Acute Opioid Withdrawal Syndrome), which may precipitate preterm labor or fetal distress. Because of this risk and because animal reproduction studies are not always predictive of human response, INJECTABLE NALOXONE HYDROCHLORIDE should be used during pregnancy only if clearly needed.

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

Pediatrics: An accidental opioid exposure is possible in the pediatric population. INJECTABLE NALOXONE HYDROCHLORIDE administration may cause an acute opioid withdrawal syndrome which may be life threatening in neonates if not recognized and properly treated (see WARNINGS AND PRECAUTIONS, Acute Opioid Withdrawal Syndrome). INJECTABLE NALOXONE HYDROCHLORIDE should be administered to a neonate only if clearly needed. As for any use of naloxone, emergency medical assistance (*i.e.*, 911) should be requested immediately, before injecting naloxone in a neonate.

ADVERSE REACTIONS

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure and tremulousness.

Hypotension, hypertension, ventricular tachycardia and fibrillation, cardiac arrest and pulmonary edema have been associated with the use of naloxone post-operatively (see WARNINGS AND PRECAUTIONS, Cardiovascular - Post-Operative).

Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

DRUG INTERACTIONS

Drug-Drug Interactions
Interactions with other drug products have not been established.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Emergency medical assistance (calling 911) should be requested immediately when an opioid overdose is suspected, before injecting naloxone (see WARNINGS AND PRECAUTIONS, Rebound Opioid Toxicity).

INJECTABLE NALOXONE HYDROCHLORIDE may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended only in emergency situations when a health care professional is present. The intramuscular route of administration is recommended for bystanders (non-health care professionals).

Since the duration of action of most opioids exceeds that of naloxone, the patient should be kept under continued surveillance and repeated doses of naloxone should be administered, as necessary (see WARNINGS AND PRECAUTIONS, Respiratory; Rebound Opioid Toxicity).

Recommended Dose and Dosage Adjustment

INJECTABLE NALOXONE HYDROCHLORIDE should be administered to neonates only if clearly needed (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Known or Suspected Opioid Overdosage

Children 0 to 1 year old

Initial Dose

An initial dose of 0.4 mg of INJECTABLE NALOXONE HYDROCHLORIDE (intravenous, intramuscular, or subcutaneous) should be administered.

Repeat Doses

If the desired degree of improvement in respiratory functions is not obtained, doses of 0.4 mg should be repeated at 2 to 3 minute intervals until the desired degree of reversal is reached. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance (see WARNINGS AND PRECAUTIONS, Respiratory).

Children over 1 year old and Adults

Initial Dose

An initial dose of 0.4 mg to 2 mg of INJECTABLE NALOXONE HYDROCHLORIDE (intravenous, intramuscular, or subcutaneous) should be administered.

A caregiver should be aware that the risk of acute opioid withdrawal syndrome will be higher in the patient receiving higher doses of naloxone. In such cases, the caregiver should be prepared for potential reactions associated with acute opioid withdrawal syndrome and to assist the patient to minimize harm when experiencing these reactions (see WARNINGS AND PRECAUTIONS, Acute Opioid Withdrawal Syndrome).

Repeat Doses

If the desired degree of improvement in respiratory functions is not obtained, doses of 0.4 mg should be repeated at 2 to 3 minute intervals until the desired degree of reversal is reached. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance (see WARNINGS AND PRECAUTIONS, Respiratory).

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics
Naloxone hydrochloride prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension. Also, it can reverse the psychosomimetic and dysphoric 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, in opioid naïve people, naloxone shows essentially no pharmacologic activity. In opioid tolerant people, naloxone may trigger an acute opioid withdrawal syndrome (see WARNINGS AND PRECAUTIONS, Acute Opioid Withdrawal Syndrome). Naloxone has not been shown to produce tolerance or to cause physical or psychological dependence.

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

STORAGE AND STABILITY

INJECTABLE NALOXONE HYDROCHLORIDE should be stored between 15 and 30°C, protected from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

INJECTABLE NALOXONE HYDROCHLORIDE 0.4 mg / mL:
Each mL of aqueous injectable solution contains: 0.4 mg naloxone hydrochloride, 8.6 mg sodium chloride, 1.8 mg methylparaben (as preservative), 0.2 mg propylparaben (as preservative), hydrochloric acid to adjust pH, and water for injection.

INJECTABLE NALOXONE HYDROCHLORIDE 1 mg / mL:
Each mL of aqueous injectable solution contains: 1 mg naloxone hydrochloride, 8.35 mg sodium chloride, 1.8 mg methylparaben (as preservative), 0.2 mg propylparaben (as preservative), hydrochloric acid to adjust pH, and water for injection.

INJECTABLE NALOXONE HYDROCHLORIDE is available as:

- 1 mL vials (0.4 mg / mL), boxes of 10 vials (discard unused portion after intervention).
- 2 mL vials (1 mg / mL), boxes of 10 vials (discard unused portion after intervention).

Latex-Free Stoppers**:** Stoppers contain no dry natural rubber.

PART II: SCIENTIFIC INFORMATION

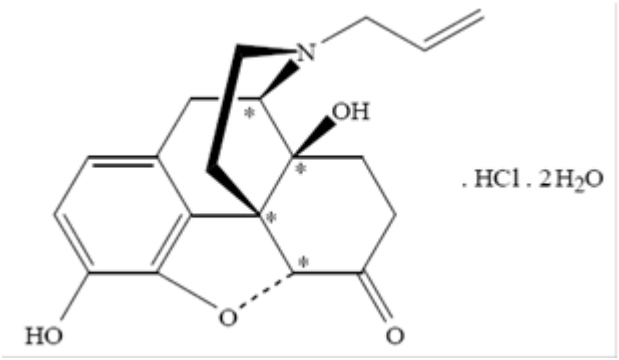
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Naloxone hydrochloride

Chemical name: 17-Allyl-4,5 α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate

Structural formula:



Molecular formula:	$C_{19}H_{21}NO_4.HCl\ 2H_2O$
Molecular mass:	363.8 g/mol anhydrous 399.9 g/mol dihydrate
Physicochemical properties:	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.

DETAILED 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 10 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, cyclazocine, 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 nontoxic 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.