NALOXONE JUNO
NALOXONE JUNO NEONATAL
(naloxone hydrochloride dihydrate injection)
DATASHEET

1. NAME OF MEDICINE

The name of this medicine is naloxone hydrochloride dihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of NALOXONE JUNO contains 440 micrograms of naloxone hydrochloride dihydrate, equivalent to 400 micrograms of naloxone hydrochloride in 1 mL of water for injections.
Each 1 mL of NALOXONE JUNO NEONATAL contains 44 micrograms of naloxone hydrochloride dihydrate, equivalent to 40 micrograms of naloxone hydrochloride in 2 mL water for injections.

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

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

NALOXONE JUNO and NALOXONE JUNO NEONATAL contain no antimicrobial preservative, therefore are for use in one patient on one occasion only; after use, any remaining solution should be discarded.

Intravenous infusion
Naloxone hydrochloride injection may be diluted for intravenous infusion in normal saline (sodium chloride solution) or 5% glucose solutions. The addition of 2 mg of naloxone hydrochloride dihydrate solution for injection in 500 mL of either solution provides a

concentration of 4 micrograms/mL. To reduced microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 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 hydrochloride injection 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 injection 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 400 micrograms to 2 mg of NALOXONE JUNO 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 10 mg of naloxone hydrochloride dihydrate have been administered, the diagnosis of opioid 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 opioid depression following the use of opioids during surgery, smaller doses of naloxone hydrochloride dihydrate are usually sufficient. The dose of naloxone hydrochloride dihydrate should be titrated according to the patient and response. For the initial reversal of respiratory depression, naloxone hydrochloride dihydrate should be injected in increments of 100 to 200 micrograms 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 dihydrate 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 dihydrate may be required at one to two hour intervals depending upon the amount, type (i.e. short or long acting) and time since last administration of opioid. 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 10 micrograms/kg body weight given intravenously. If this dose does not result in the desired degree of clinical improvement a subsequent dose of 100 micrograms/kg body weight may be administered. If the intravenous route of administration is not available, naloxone hydrochloride dihydrate may be administered by intramuscular or subcutaneous injection in divided doses. If necessary naloxone hydrochloride injection can be diluted with Water for Injections.

Postoperative Narcotic Depression. Follow the recommendations and cautions under Adult Postoperative Depression. For the initial reversal of respiratory depression. Naloxone hydrochloride dihydrate should be injected in increments of 5 micrograms to 10 micrograms intravenously at two to three minute intervals to the desired degree of reversal.

Usage in Neonates

Narcotic-induced Depression. The usual initial dose is 10 micrograms/kg body weight administered by intravenous, intramuscular or subcutaneous injection. This dose may be repeated in accordance with the adult administration guidelines for postoperative opioid depression.

4.3 Contraindications

NALOXONE JUNO and NALOXONE JUNO NEONATAL are contraindicated in patients known to be hypersensitive to naloxone hydrochloride dihydrate or to any other ingredients in NALOXONE JUNO and NALOXONE JUNO NEONATAL.

4.4 Special warnings and precautions for use

Naloxone hydrochloride dihydrate should be administered cautiously to persons including newborns of 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 withdrawal syndrome.

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

Naloxone hydrochloride dihydrate is not effective against respiratory depression due to non-opioid drugs.

In addition to naloxone hydrochloride dihydrate, 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, pulmonary oedema have been reported in post-operative patients following naloxone hydrochloride dihydrate administration. These have occurred in postoperative patients most of whom had preexisting 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 dihydrate should be used with caution in patients with preexisting cardiac disease or patients who have received medications with potential adverse cardiovascular effects.

4.5 Interaction with other medicines and other forms of interaction

The effect of naloxone hydrochloride dihydrate is based on the interaction with opioids and opioid agonists, reversing effects of opioids; rapid reversal may precipitate acute withdrawal syndrome in opioid dependence. At the usual naloxone hydrochloride dihydrate dose there is no interaction with barbiturates and tranquillizers. Data on the interaction with alcohol are not uniform. In patients with multiple intoxication with opioids and sedatives or alcohol, the result of naloxone hydrochloride dihydrate administration may be delayed, dependent on the cause of intoxication.

Complete analgesia can be restored following administration of naloxone hydrochloride dihydrate to patients that had buprenorphine as analgesic. It is assumed that this effect is caused by the arched form of the dose-response curve of buprenorphine with decreasing analgesia at

(too) high doses. However, reversal of respiratory depression caused by buprenorphine is limited.

Naloxone hydrochloride 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.

Naloxone hydrochloride dihydrate 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 hydrochloride dihydrate is used postoperatively to reverse the central depressive effects of opioid agonists used as anaesthesia adjuncts, the dose of naloxone hydrochloride dihydrate must be carefully titrated to achieve the desired effect without interfering with control of postoperative pain, or causing other adverse effects.

4.6 Fertility, pregnancy and lactation

Carcinogenesis, mutagenesis, impairment of fertility.

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

Use in Pregnancy

Category B1.

Teratogenic effects. Reproduction studies performed in mice and rats at high subcutaneous doses, revealed no evidence of impaired fertility or harm to the foetus due to naloxone hydrochloride dihydrate. 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 dihydrate should, therefore, be administered to pregnant patients only when, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Use in Lactation

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

4.7 Effects on ability to drive and use machines

Naloxone hydrochloride 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

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 Special warnings and precautions for use in Adults Postoperative Narcotic Depression). Seizures have been

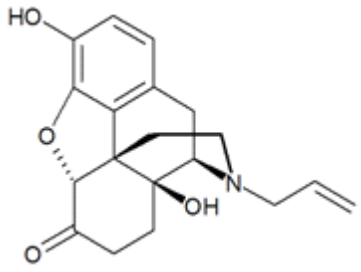
reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

4.9 Overdose

There is no clinical experience with naloxone hydrochloride overdosage in humans. In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injection, no toxic effects were seen at 10 mg/kg/day for 3 weeks.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties



$HCl \cdot 2H_2O$

Chemical name: (4,5α-Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dihydrate
Molecular formula: $C_{19}H_{22}ClNO_4.2H_2O$
Molecular weight: 399.87
CAS registry number: 51481-60-8

Naloxone hydrochloride, a narcotic agonist, is a synthetic congener of oxymorphone.

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

Naloxone hydrochloride dihydrate has not been shown to produce tolerance or to cause physical or psychological dependence. In the presence of physical dependence on opioids, naloxone hydrochloride dihydrate will produce withdrawal symptoms. While the mechanism of action of naloxone hydrochloride dihydrate is not fully understood, the preponderance of evidence suggests that naloxone hydrochloride dihydrate antagonises the opioid effects by competing for the same receptor sites.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Following parenteral administration, naloxone hydrochloride dihydrate is rapidly distributed in the body.

Metabolism and excretion

Naloxone hydrochloride dihydrate 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Hydrochloric acid (pH adjustor) qs pH 3.0 – 3.3

6.2 Incompatibilities

No drug or chemical agent should be added to NALOXONE JUNO or NALOXONE JUNO NEONATAL unless its effect on the chemical and physical stability of the solution has first been established. NALOXONE JUNO and NALOXONE JUNO NEONATAL should not be mixed with preparations containing sulfite, metabisulfite, long chain or high molecular weight anions, or any solution having an alkaline pH.

6.3 Shelf life

24 months when stored below 25°C.

6.4 Special precautions for storage

Protect from light.

6.5 Nature and contents of container

NALOXONE JUNO: naloxone hydrochloride dihydrate 400 micrograms / 1 mL in clear glass ampoules (pack sizes – 1, 5 and 10 ampoules).
NALOXONE JUNO NEONATAL: naloxone hydrochloride dihydrate 40 micrograms / 2 mL in clear glass ampoules (pack sizes – 1, 5 and 10 ampoules)

MEDICINE SCHEDULE

Prescription medicine

NAME AND ADDRESS OF SPONSOR

Juno Pharmaceuticals NZ Pty Ltd
L3, Nexia Centre,
22 Amersham Way,
Manukau,
Auckland,
New Zealand

DATE OF FIRST APPROVAL

12 July 2018

DATE OF REVISION OF THE TEXT

TBD