

1 NAME OF THE MEDICINAL PRODUCT

Naloxone Hydrochloride 1mg/ml Solution for Injection in a pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Naloxone Hydrochloride 1 mg/ml

Excipient with known effect:

1 ml of Naloxone hydrochloride contains 3.497 mg of sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

An isotonic, sterile Solution for Injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Naloxone may be used for the complete or partial reversal of opioid depression, including mild to severe respiratory depression induced by natural and synthetic opioids, including dextropropoxyphene, methadone and certain mixed agonist/antagonist analgesics: nalbuphine and pentazocine. It may also be used for the diagnosis of suspected acute opioid overdose. Naloxone may also be used to counteract respiratory and other CNS depression in the new-born resulting from the administration of analgesics to the mother during childbirth.

4.2 Posology and method of administration

Intravenous infusion: Naloxone may be diluted for intravenous infusion in normal saline (0.9%) or 5% dextrose in water or saline: the addition of 2mg (2ml of 1mg/1ml concentration)

of Naloxone in 500ml of either solution provides a concentration of 4 micrograms/ml. Mixtures should be used within 12 hours. After 12 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response to both Naloxone infusion and to any previous bolus doses administered.

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

Adults:

Opioid overdose (known or suspected)

An initial dose of 400 to 2000 micrograms of Naloxone may be administered intravenously. If the desired degree of counteraction and improvement in respiratory function is not obtained it may be repeated at 2 to 3 minute intervals. If no response is observed after 10mg of Naloxone have been administered the diagnosis of opioid-induced or partial opioid induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if dosing by the intravenous route is not feasible.

N.B. The duration of action of certain opioids can outlast that of an IV bolus of Naloxone, e.g. dextropropoxyphene (present in commonly prescribed analgesics which in over-dosage have been associated with suicide), dihydrocodeine and methadone. In situations where one of these opioids is known or suspected it is recommended that an infusion of Naloxone be used to produce sustained antagonism to the opioid without repeated injection.

Post Operative Use

When Naloxone is used postoperatively, the dose should be titrated for each patient in order to obtain optimum respiratory response while maintaining adequate analgesia. Intravenous doses of 100-200 micrograms (approximately 1.5-3 micrograms/kg body weight) are usually sufficient, but a full two minutes should be allowed between each 100 micrograms increment of Naloxone administered. Further intramuscular doses may be needed within one to two hours, depending on the interval since the last opioid administration and the amount and type (i.e. long or short-acting) of drug used. Alternatively Naloxone may be administered as an intravenous infusion (see above).

Paediatric population

The usual initial dose in children is 10 micrograms/kg body weight given i.v. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 100 micrograms/kg of bodyweight may be administered. Naloxone may be required by infusion as described above. If an i.v. route of administration is not feasible, Naloxone may be administered i.m. or s.c. in divided doses.

Neonatal Use

An adequate airway should be established in the apnoeic infant before Naloxone is administered. The usual dose is for opioid-induced depression is 10 micrograms/kg body weight administered i.v., i.m., or s.c.. If the desired degree of counteraction and improvement in respiratory function is not obtained it may be repeated at 2-3 minute intervals. Alternatively, a single dose of 200 micrograms, approximately 60 micrograms/kg body weight may be given intramuscularly at birth.

It should, however, be noted that onset of action is slower following i.m. injection. In neonates needing infusion of Naloxone in saline, care should be taken to avoid excessive sodium intake.

Elderly

There have been no specific studies for use in the elderly.

Method of administration

Naloxone is for intravenous, intramuscular or subcutaneous injection or intravenous infusion.

4.3 Contraindications

Naloxone should not be given to patients who are known to be hypersensitive to the drug or any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

It should be administered cautiously to patients who have received large doses of opioids or to those physically dependent on opioids since too rapid reversal of opioid effects by Naloxone may precipitate an acute withdrawal syndrome in such patients. The same caution is needed when giving Naloxone to neonates delivered of such patients.

Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest have been described.

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, piloerection, sweating, yawning, nausea, vomiting, nervousness, restlessness, irritability, shivering, 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 responded satisfactorily to Naloxone should be kept under observation. Repeated doses of Naloxone may be necessary since the duration of action of some opioids may exceed that of Naloxone.

Naloxone is not effective against respiratory depression caused by non-opioid drugs. Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs, respiration should be mechanically assisted.

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

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary oedema and cardiac arrest have been reported in postoperative patients. 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 medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation and pulmonary oedema.

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 poisoning.

Renal Insufficiency/Failure: The safety and effectiveness of Naloxone in patients with renal insufficiency/failure have not been established in clinical trials. Caution should be exercised and patients monitored when Naloxone is administered to this patient population.

Liver disease: The safety and effectiveness of Naloxone in patients with liver disease have not been established in well-controlled clinical trials. In one small study in patients with liver cirrhosis, plasma naloxone concentrations were approximately six times higher than in patients without liver disease. Naloxone administration had a diuretic effect in these patients with cirrhosis. Caution should be exercised when Naloxone is administered to a patient with liver disease.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The effect of naloxone hydrochloride is due to the interaction with opioids and opioid agonists. When administered to subjects dependent on opioids, in some subjects the administration of naloxone hydrochloride can cause pronounced withdrawal symptoms. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest have been described.

With a standard naloxone hydrochloride dose there is no interaction with barbiturates and tranquillizers.

Data on interaction with alcohol are not unanimous. In patients with multi intoxication as a result of opioids and sedatives or alcohol, depending on the cause of the intoxication, one may possibly observe a less rapid result after administration of naloxone hydrochloride.

When administering naloxone hydrochloride to patients who have received buprenorphine as an analgesic complete analgesia may be restored. It is thought that this effect is a result of the arch-shaped dose-response curve of buprenorphine with decreasing analgesia in the event of high doses. However, reversal of respiratory depression caused by buprenorphine is limited.

Severe hypertension has been reported on administration of naloxone hydrochloride in cases of coma due to a clonidine overdose.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established.

Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. The medicinal product should not be used during pregnancy unless clearly necessary.

In a pregnant woman who is known or suspected to be opioid-dependent, risk benefit must be considered before Naloxone is administered, since maternal dependence may be accompanied by foetal dependence. In this type of circumstance, the neonate should be monitored for respiratory rate and signs of opioid withdrawal.

Use in Labour and Delivery

Naloxone may be administered to mothers during the second stage of labour to correct respiratory depression caused by opioids used to provide obstetrical analgesia.

It is not known if Naloxone affects the duration of labour and/or delivery.

Breast-feeding

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 mother. Therefore, breast-feeding should be avoided for 24 hours after treatment.

4.7 Effects on ability to drive and use machines

Patients who have received naloxone hydrochloride to reverse the effects of opioids should be warned to avoid road traffic, operate machinery or engage in other activities demanding physical or mental exertion for at least 24 hours, since the effect of the opioids may return.

4.8 Undesirable effects

The following frequency terminology is used:

Very common: $\geq 1/10$;

Common: $\geq 1/100$, $< 1/10$;

Uncommon: $\geq 1/1,000$, $< 1/100$;

Rare: $\geq 1/10,000$, $< 1/1,000$;

Very rare: $< 1/10,000$;

Not known (cannot be estimated from the available data)

Immune system disorders

Very rare: Allergic reactions (urticaria, rhinitis, dyspnoea, Quincke's oedema), anaphylactic shock

Nervous system disorders

Common: Dizziness, headache

Uncommon: Tremor, sweating

Rare: Seizures, tension

Seizures have occurred rarely following administration of naloxone hydrochloride; however, a causal relationship to the drug has not been established. Higher than recommended dosage in postoperative use can lead to tension.

Cardiac disorders

Common: Tachycardia

Uncommon: Arrhythmia, bradycardia

Very rare: Fibrillation, cardiac arrest

Vascular disorders

Common: Hypotension, hypertension Hypotension, hypertension and cardiac arrhythmia (including ventricular tachycardia and fibrillation) have also occurred with the postoperative use of naloxone hydrochloride. Adverse cardiovascular effects have occurred most frequently in

postoperative patients with a pre-existing cardiovascular disease or in those receiving

other drugs that produce similar adverse cardiovascular effects.

Respiratory, thoracic and mediastinal disorders

Very rare: Pulmonary oedema

Pulmonary oedema has also occurred with the postoperative use of naloxone hydrochloride.

Gastrointestinal disorders

Very common: Nausea

Common: Vomiting

Uncommon: Diarrhoea, dry mouth

Nausea and vomiting have been reported in postoperative patients who have received doses higher than recommended. However, a causal relationship has not been established, and the symptoms may be signs of too rapid antagonisation of the opioid effect.

Skin and subcutaneous tissue disorders

Very rare: Erythema multiforme

One case of erythema multiforme cleared promptly after naloxone hydrochloride was discontinued.

General disorders and administration site conditions

Common: Postoperative pain

Uncommon: Hyperventilation, irritation of vessel wall (after i.v. administration); local irritation and inflammation (after i.m. administration)

Higher than recommended dosage in postoperative use can lead to the return of pain.

A fast reversal of opioid effect can induce hyperventilation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is limited clinical experience with Naloxone overdosage in humans.

Adult Patients: In one study, volunteers and morphine-dependent subjects who received a single subcutaneous dose of 24mg/70kg did not demonstrate toxicity.

In another study, 36 patients with acute stroke received a loading dose of 4mg/kg (10mg/m²/min) of Naloxone followed immediately by 2mg/kg/hr for 24 hours. There were a few reports of serious adverse events: seizures (2 patients), severe hypertension (1) and hypotension and/or bradycardia (3).

At doses of 2 mg/kg in normal subjects, memory impairment has been reported.

Paediatric Patients: Up to 11 doses of 0.2mg of naloxone (2.2mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulphate. Paediatric reports include a 2½ year old child who inadvertently received a dose of 20mg of naloxone and a 4½ year old child who received 11 doses during a 12-hour period, both of whom had no adverse sequelae.

Patient Management: Patients who experience a Naloxone overdose should be treated symptomatically in a closely-supervised environment. Physicians should contact a poison control centre for the most up-to-date patient management information.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidotes

ATC-Code: V03AB15

Naloxone is a competitive antagonist of μ , δ and κ -opioid receptors. Naloxone is most potent at the μ -receptor. Naloxone, given on its own, produces very little effect. However, if it is given in higher doses it rapidly reverses the effect of morphine and other opioids, including pentazocine and nalorphine. Naloxone has little effect on the pain threshold in normal conditions, but causes hyperalgesia in stressful conditions where endogenous opioids are produced. Naloxone also inhibits acupuncture analgesia, which is associated with the release of opioid peptides. Naloxone also prevents analgesia produced by PAG (periaqueductal grey matter) stimulation. PAG is one site of action in pain transmission. Naloxone is given intravenously and its effects are produced immediately. It is rapidly metabolised by the liver, and its effect lasts only 1-2 hours, which is a lot shorter than that of most morphine-like drugs. Thus it may have to be given repeatedly.

5.2 Pharmacokinetic properties

Absorption

Naloxone is rapidly absorbed following oral administration but high presystemic metabolism makes this route unreliable. Although the drug is effective orally, doses much larger than those required for parenteral administration are required for complete opioid antagonism.

Therefore, naloxone hydrochloride is administered parenterally.

Distribution

Naloxone is highly lipid soluble and is thus rapidly distributed throughout the body, with a volume of distribution of 5.1 kg^{-1} . High concentrations occur in brain, kidney, lung, heart and skeletal muscle. The brain/serum ratio has been estimated to be 1.5-4.6, approximately 15 times that of morphine. In adult humans, the distribution volume at steady-state is reported to be about 2 l/kg. Protein binding is within the range of 32 to 45 %.

Levels of naloxone in the central nervous system are short-lived as rapid redistribution occurs and this could account for the short duration of action. About 50% of naloxone is bound to plasma proteins, principally albumin. The plasma half-life is 1-2 hours. Naloxone hydrochloride readily crosses the placenta; however, it is not known whether naloxone hydrochloride is distributed into breast milk.

Metabolism

When naloxone reaches the liver it undergoes extensive biotransformation, mainly by conjugation with glucuronic acid, almost none of the drug excreted being unchanged and excreted in urine.

Elimination

Metabolites are excreted largely in the urine, 70% of the dose being recoverable over 72 hours. In the neonate the elimination half-life is prolonged because of reduced hepatic metabolism. The total body clearance amounts to 22 ml/min/kg.

5.3 Preclinical safety data

Preclinical data did not reveal a special hazard for humans, based on conventional studies of acute and repeated dose toxicity.

Naloxone hydrochloride was weakly positive in the Ames mutagenicity and in vitro human lymphocyte chromosome aberration tests and was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in an in vivo rat bone marrow chromosome aberration study.

Studies to determine the carcinogenic potential of naloxone hydrochloride have not been performed to date.

Dose-dependent changes in the speed of postnatal neurobehavioral development and abnormal cerebral findings have been reported in rats after in utero exposure.

In addition, increases in neonatal mortality and reduced body weights have been described after exposure during late gestation in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Dilute Hydrochloric Acid

Water for Injections

Nitrogen

6.2 Incompatibilities

It is recommended that infusions of Naloxone Hydrochloride should not be mixed with preparations containing bisulphite, metabisulphite, long-chain or high molecular weight anions, or solutions with an alkaline pH

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container in order to protect from light.

6.5 Nature and contents of container

Sterile solution for injection presented in a Glass (Type I) 2ml prefilled syringe.

6.6 Special precautions for disposal and other handling

Use once and discard any remaining solution.

7 MARKETING AUTHORISATION HOLDER

Aurum Pharmaceuticals Ltd

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RM3 8UG

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8. MARKETING AUTHORISATION NUMBER(S)

PL 12064/0060

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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12/11/2019