

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prenoxad 1mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is Naloxone Hydrochloride 1 mg/ml
1 ml of solution - contains 1 mg of naloxone hydrochloride.
For a full list of excipients, see section 6.1.

Excipients with known effect:

Each 2 ml of solution contains 0.018g of sodium chloride

3. PHARMACEUTICAL FORM

Solution for injection/infusion in a pre-filled syringe

Sterile, clear and colourless liquid with a pH of 3.0-4.0 and osmolarity
270 to 300 mOsmol/L

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prenoxad Injection is intended for emergency use in the home or other non-medical setting by appropriate individuals or in a health facility setting for the complete or partial reversal of respiratory depression induced by natural and synthetic opioids, including methadone, diamorphine (diacetylmorphine (INN)) and certain other opioids such as dextropropoxyphene and certain mixed agonist/antagonist analgesics: nalbuphine and pentazocine.

For this reason Prenoxad Injection should be carried by persons at risk of such events.

It may also be used for the diagnosis of suspected acute opioid overdose.

4.2. Posology and method of administration

Prenoxad Injection may only be made available once the prescriber has assessed the suitability and competence of a client or representative to administer naloxone in the appropriate circumstances.

Prenoxad Injection is for administration by intramuscular injection.

Prenoxad Injection is administered as a part of a resuscitation intervention in suspected overdose casualties, where opioid drugs may be involved or suspected. It may need to be used in a non-medical setting. Therefore, the prescriber should take appropriate steps to ensure that the patient thoroughly understands the indications and use of Prenoxad Injection. The prescriber should review with the patient or any other person who might be in a position to administer Prenoxad Injection to a patient experiencing a suspected opioid overdose event.

In patients where breathing does not appear to be normal

In patients where breathing does not appear to be normal administration of Prenoxad Injection should be preceded by calling emergency services and requesting an ambulance. Following this, 30 chest compressions and if possible 2 rescue breaths (Basic Life Support SINGLE CYCLE) should be given; 0.4ml Prenoxad Injection solution should then be administered by intramuscular injection into

the outer thigh muscle or muscles of the upper arm, through clothing if necessary. A further 3 cycles of chest compressions and rescue breaths should then be given followed by administration of 0.4ml Prenoxad Injection. Three cycles of chest compression and rescue breaths should take approximately 2 minutes. This should be repeated until an ambulance arrives or the patient begins breathing normally / regains consciousness. The patient when breathing normally or has regained consciousness should be placed in the recovery position (lying on their side, mouth open pointing towards the ground) and observed continuously.

In patients where breathing is normal but the patient is unresponsive or suspected to be unconscious.

Patient should be placed in the recovery position (lying on their side, mouth open pointing towards the ground). 0.4ml Prenoxad Injection solution should be administered by intramuscular injection into the outer thigh muscle or muscles of the upper arm, through clothing if necessary, and an ambulance should be called, 0.4ml Prenoxad Injection solution should then be administered every 2-3 minutes and continued until the ambulance arrives and/or the patient regains consciousness. The patient should be continuously observed but particularly their breathing. If there is a decrease in breathing it is important that 0.4ml Prenoxad Injection solution is given every 2-3 minutes.

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

Adults:

Opioid overdosage (known or suspected)

Use by individuals in the community

400 micrograms or 0.4ml of Prenoxad Injection solution by intramuscular injection into the outer thigh or muscles of the upper arm as part of the resuscitation intervention. The dose of 0.4ml can be repeated every 2-3 minutes in subsequent resuscitation cycles until the contents of a syringe are used up.

N.B. The duration of action of certain opioids can outlast that of an IV bolus of Naloxone, e.g. dextropropoxyphene, 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.

Children

The Prenoxad Injection presentation is not intended to be used for children in the home setting other than by an appropriately trained healthcare professional. In the event of a child being given or taking an opioid inadvertently an ambulance should be called and resuscitation started if required.

Neonatal Use

Naloxone should only be used in Neonates under medical supervision.

Elderly

Use as for adults.

4.3. Contraindications

Prenoxad Injection should not be given to patients who are known to be hypersensitive to the drug or any of the ingredients

4.4. Special warnings and precautions for use

Patients must be instructed in the proper use of Prenoxad Injection. See Section 4.3.

Prenoxad Injection is intended as an emergency treatment and the patient should be advised to seek medical help immediately. Therefore patients at risk of experiencing an opioid overdose event and/or any other person who might be in a position to administer Prenoxad Injection to a patient experiencing such an event should be carefully instructed in regard to the circumstances under which this potentially life-saving medication should be used.

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 Prenoxad Injection may precipitate an acute withdrawal syndrome in such patients.

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 Prenoxad Injection should be placed under medical supervision and kept under observation for at least 2 hours. Repeated doses of Prenoxad Injection may be necessary since the duration of action of some opioids may exceed that of Prenoxad Injection.

Prenoxad Injection 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 sequel of these events. Although a direct cause and effect relationship has not been established, Prenoxad Injection 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 Prenoxad Injection 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 Prenoxad Injection in patients with renal insufficiency/failure have not been established in clinical trials. Caution should be exercised and patients monitored when Prenoxad Injection is administered to this patient population.

Liver disease: The safety and effectiveness of Prenoxad Injection 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 Prenoxad Injection is administered to a patient with liver disease.

4.5. Interaction with other medicinal products and other forms of interaction

Prenoxad Injection should be administered cautiously to persons including new-borns of 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.

4.6. Pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri- and postnatal development. Prenoxad Injection should, like all drugs, be used with caution during pregnancy.

In a pregnant woman who is known or suspected to be opioid-dependent, risk benefit must be considered before Prenoxad Injection 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 Injection 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.

Lactation

It is not known whether Naloxone is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when Prenoxad Injection is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8. Undesirable effects

The following frequency terminology is used:

Very common: 1/10;

Common: 1/100, < 1/10;

Uncommon: 1/1,000, < 1/100;

Rare: 1/10,000, < 1/1,000;

Very rare: < 1/10,000;

Not known (cannot be estimated from the available data)

System Organ Class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations						Fever ³
Immune system disorders					Allergic reactions (urticaria, rhinitis, dyspnoea, Quincke's oedema), anaphylactic shock	
Psychiatric disorders						Nervousness ³ , restlessness ³ , irritability ³
Nervous system disorders		Dizziness, headache	Tremor, sweating	*Seizures Tension		
Cardiac disorders		~Ventricular tachycardia ^{1,2}	~Arrhythmia ^{1,2} bradycardia ^{1,2}		~Fibrillation ^{1,2} ~cardiac arrest ^{1,2}	
Vascular disorders		~Hypotension ¹ ~hypertension ²				Dyspnoea ¹
Respiratory, thoracic and mediastinal disorders					pulmonary oedema when used in postoperative patients	Runny nose and sneezing ³ , yawning ³
Gastrointestinal disorders	Nausea ⁴	Vomiting ⁴	Diarrhoea ³ , dry mouth			
Skin and subcutaneous tissue disorders					Erythema multiforme One case of erythema multiforme cleared promptly after naloxone hydrochloride was discontinued.	Piloerection ³
Musculoskeletal and connective tissue disorders						Weakness ³ , shivering ³
General disorders and administration site conditions		Postoperative pain	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			Death when used in postoperative patients or when reversal of opioid depression is abrupt
Investigations						Increased blood pressure when reversal of opioid depression is abrupt
Injury, poisoning and procedural complications						Agitation when administered in excessive doses to postoperative patients
Surgical and medical procedures						reversal of analgesia when administered in excessive doses to postoperative patients

¹ when used in postoperative patients

² when used in the abrupt reversal of opioid depression (see Special Warnings)

³ symptom of acute withdrawal syndrome, in case of abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate (see Special Warnings)

⁴ 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 antagonism of the opioid effect.

*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.

⁵Hypotension, 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.

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 Prenoxad Injection 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

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

Naloxone is rapidly absorbed following oral administration but high presystemic metabolism makes this route unreliable. Naloxone is highly lipid soluble and is thus rapidly distributed throughout the body, with a volume of distribution of 5.1kg -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. 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. When naloxone reaches the liver it undergoes extensive biotransformation, almost none of the drug excreted being unchanged. 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.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to the prescriber which is additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Dilute Hydrochloric Acid (for pH adjustment)
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 (Martindale, 1996).

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

Sterile solution for injection presented in a Glass (Type I) 2ml prefilled syringe. The pack contains two 23G x 1¼" needles.

6.6 Instruction for use, handling and disposal Single patient use only.

Discard any unused solution immediately after use. Any unused product or waste material (including needles) should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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