SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

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 the full list of excipients, see section 6.1.

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, 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

Posology
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 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 were breathing is normal but the patient is unrousable 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 inappropriately 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.

Method of administration
Prenoxad Injection is for administration by intramuscular injection.

4.3 Contraindications

Prenoxad Injection 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

Patients must be instructed in the proper use of Prenoxad Injection . See Section 4.2.

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 same caution is needed when giving Prenoxad to neonates delivered to 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 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.

1 ml of naloxone hydrochloride contains 3.497 mg of sodium which is 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 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

Prenoxad 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.

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 Prenoxad Injection is administered to a nursing mother. Therefore, breast-feeding should be avoided in the first 24 hours after treatment.

4.7 Effects on ability to drive and use machines

Patients who have received Prenoxad 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: (≥1/10)>
Common: (≥1/100 to <1/10)>Uncommon: (≥1/1,000 to <1/100)>Rare: (≥1/10,000 to <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/m^2/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

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 5.1kg -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. 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 (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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Keep the syringe in the plastic box in order to protect from light.

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 Special precautions for disposal and other handling

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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8 MARKETING AUTHORISATION NUMBER(S)

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