Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prenoxad 0.91 mg/ml solution for injection in a pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is naloxone hydrochloride
1 ml of solution for injection – contains 1mg of naloxone hydrochloride dihydrate equivalent to 0.91mg of naloxone hydrochloride.

Excipients with known effect:
Each 2 ml of solution contains 0.018g of sodium chloride

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection 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 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 central nervous system depression, especially with concomitant respiratory depression, induced by natural or synthetic opioids. For diagnosis of suspected acute opioid overdose.
- Use in adults and adolescents aged 16 years or over.
- Children and neonates. This product is not indicated in these patient populations in the home or non-medical setting.

4.2 Posology and method of administration

Posology
Prenoxad may be made available once the prescriber has assessed the suitability and competence of an individual to administer naloxone in the appropriate circumstances.
Prenoxad is for administration by intramuscular injection.
Prenoxad 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* as per local clinical guidance should take appropriate steps to ensure that the patient thoroughly understands the indications and use of Prenoxad. *The prescriber* as per local clinical guidance should review the content of Prenoxad training module with the patient or any other person who might be in a position to administer Prenoxad.
Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

If the patient does not appear to be breathing normally: If the patient is not breathing normally (i.e. you have not detected 1 or 2 breaths/breathing in the casualty during the 10 second assessment):

1. Call the emergency services immediately and ask for an ambulance, explaining that the patient is unconscious and not breathing normally
2.Give basic life support by giving 3 cycles of 30 chest compressions and 2 rescue breaths if possible.
3.Give one dose (0.4 ml) of Prenoxad;
o Open and assemble Prenoxad
oHold the syringe like a pen

oInject the patient with Prenoxad. The needle should be inserted into the patient's outer thigh or upper arm muscle at a right angle to the surface of the skin, straight through clothing if required
o Push the plunger to the first black line
oWithdraw the needle from the patient's outer thigh or upper arm muscle and put the syringe (with the needle still attached) back into the 'cradle' in the Prenoxad case. It will fit into the cradle even with the needle attached.
oDo not attempt to remove or re-sheath the needle
4. If the patient is still not breathing normally, give 3 more sets of 30 chest compressions and 2 rescue breaths followed by one dose of 0.4 ml of Prenoxad. Inject Prenoxad following the same process and using the same needle as before. Repeat this as many times as necessary until:
oThe patient starts breathing normally
oThe ambulance arrives.
5.When the patient is breathing normally move them to the recovery position, lying on their side, mouth open and pointing towards the ground. Stay with the patient and continue to monitor their breathing.
If the patient is breathing normally but is unrousable or unconscious: If the patient is breathing normally (i.e. you have detected 1 or 2 breaths/ breathing in the patient during the 10 second assessment) but is unconscious or not rousable (i.e. can't be woken up):
1.Move the patient into the recovery position, lying on their side, mouth open and pointing towards the ground
2.Give one dose (0.4 ml) of Prenoxad:
oOpen and assemble Prenoxad
oHold the syringe like a pen
oInject the patient with Prenoxad. The needle should be inserted into the patient's outer thigh or upper arm muscle at a right angle to the surface of the skin, straight through clothing if required
oPush the plunger to the first black line
oWithdraw the needle from the patient's thigh or upper arm muscle and put the syringe (with the needle still attached) back into the 'cradle' in the Prenoxad case. It will fit into the cradle even with the needle attached.
o Do not attempt to remove or re-sheath the needle
3.Call the emergency services and ask for an ambulance explaining that you have a patient who is unconscious but appears to be breathing
4.If the patient does not wake up/regain consciousness, keep them in the recovery position and give further doses of Prenoxad every 2 to 3 minutes. Inject Prenoxad following the same process and using the same needle as before i.e. hold the syringe like a pen, inject at a right angle to the surface of the skin and push the plunger down to the next black line. Repeat this as many times as necessary until:
oThe patient regains consciousness
oThe ambulance arrives

5.Stay with the patient and continue to monitor their breathing. If there is a decrease in breathing give 0.4 ml of Prenoxad every 2 -3 minutes. If the patient's breathing becomes less frequent or stops, you may need to give basic life support

Adults:
Opioid overdosage (known or suspected)
Use by individuals in the community
400 micrograms or 0.4 ml of Prenoxad by intramuscular injection into the outer thigh or muscles of the upper arm as part of the resuscitation intervention. The dose of 0.4 ml can be repeated every 2-3 minutes in subsequently resuscitation cycles until the contents of a syringe are used up.
N.B. The duration of action of certain opioids, e.g. dihydrocodeine and methadone can outlast that of an intramuscular dose of naloxone. 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. This will be in a healthcare setting.
Children:
This product is not indicated in this patient population in the home setting. 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:
This product is not indicated in this patient population in the home setting.
Elderly:
Use as for adults.
Patients with renal impairment:
The safety and effectiveness of Prenoxad in patients with renal insufficiency/failure have not been established in clinical trials. Caution should be exercised and patients monitored when Prenoxad solution for injection/infusion in a pre-filled syringe is administered to this patient population.
Patients with hepatic impairment:

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

Method of administration:

Prenoxad is a sterile solution for injection presented in a 2 ml prefilled graduated syringe. The pack contains two needles. Prenoxad is used after connecting one needle to the syringe (as explained pictorially in the Patient Leaflet) by inserting the needle into the patient's outer thigh or upper arm, through clothing if necessary, and by injecting a first dose (0.4ml). The needle and syringe have to be withdrawn after each dose and the syringe should be returned to the retaining cradle within the Prenoxad box. The needle should not be re-sheathed. If another dose is deemed necessary, the syringe has to be inserted again followed by injection of one dose (to the next black line). The second needle is provided as a back-up should the first become damaged for example when puncturing through thick clothing or the content of pockets in an emergency.

The prescriber as per local clinical guidance is responsible for ensuring that the individual can access suitable training such that they understand how and when to administer Prenoxad.

4.3 Contraindications

Prenoxad is contraindicated in patients with hypersensitivity to naloxone hydrochloride dihydrate or to any of the excipients of this medicinal product listed in section 6.1.

4.4 Special warnings and precautions for use

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

Prenoxad 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 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.

Prenoxad must be given with caution to patients who have received large doses of opioids or are physically dependent on opioids. Too rapid reversal of the opioid effect can cause withdrawal syndrome in such patients. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest have been described.

This also applies to new born infants of such patients.

Patients who respond satisfactorily to naloxone must be carefully monitored. The effect of opioids can be longer than the effects of naloxone, and new injections may be necessary.

Naloxone is not effective in central depression caused by agents other than opioids. Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs, respiration should be mechanically assisted.

Naloxone has been reported to induce hypotension, hypertension, ventricular tachycardia, fibrillation and pulmonary oedema. These adverse effects have been observed in patients who have cardiovascular diseases or who have used medicines with similar cardiovascular adverse effects. Although no direct causative relations have been shown, caution should be used in administrating Prenoxad to patients with heart diseases or to patients who are taking relatively cardiotoxic drugs causing ventricular tachycardia, fibrillation and cardiac arrest (e.g. cocaine, methamphetamine, cyclic antidepressants, calcium channel blockers, beta blockers, and digoxin). See Section 4.8.

Prenoxad is used in patients to reverse the effects of opioid overdose which in itself will have a major influence on the ability to drive and use machines.

This product contains less than 1 mmol sodium (23 mg) per 2 ml dose and it is essentially "sodium-free".

In addition to Prenoxad Injection other resuscitative measures such as maintenance of a free airway, artificial ventilation and cardiac massage should be employed when necessary in opioid overdose patients.

Renal Insufficiency/Failure: The safety and effectiveness of Prenoxad in patients with renal insufficiency/failure have not been established in clinical trials. Caution should be exercised and patients monitored when Prenoxad is administered to this patient population (see section 4.2).

Liver disease: The safety and effectiveness of Prenoxad 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 is administered to a patient with liver disease (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

The effect of Prenoxad is due to the interaction with opioids and opioid agonists. When administered to subjects dependent on opioids, in some subjects Prenoxad can produce withdrawal symptoms. Hypertension, cardiac arrhythmia, pulmonary oedema and cardiac arrest have been described.
With a standard Prenoxad dose there is no interaction with barbiturates and tranquillizers e.g. benzoediazepines and antipsychotics.
Data on interactions 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 Prenoxad. Reversal of respiratory depression caused by buprenorphine may be limited.
Severe hypertension has been reported on administration of naloxone in cases of coma due to a clonidine overdose.
Prenoxad 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 narcotic effects may precipitate an acute abstinence syndrome.

4.6 Fertility, pregnancy and lactation

Fertility
Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no adverse effect of naloxone on fertility.

Pregnancy
For naloxone insufficient data on exposed pregnancies are available.
Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. This medicinal product should not be used during pregnancy unless clearly necessary.
Naloxone can cause withdrawal symptoms in newborn infants (see section 4.4).

Breast-feeding
It is not known whether naloxone passes into breast milk and it is not established whether infants who are breast-fed are affected by naloxone. Therefore, breast-feeding should be avoided in the first 24 hours after treatment.

4.7 Effects on ability to drive and use machines

Prenoxad is used in patients to reverse the effects of opioid overdose which in itself will have a major influence on the ability to drive and use machines.
Since the effect of the opioid may return (see section 4.4), patients should be warned not to take part in road traffic or operate machinery.

4.8 Undesirable effects

The following frequency terminology is used:

Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1000 to <1/100)
Rare (≥ 1/10 000 to <1/1000)
Very rare (<1/10000)
Not known (cannot be estimated from available data)

System Organ Class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations						Fever[2]
Immune system disorders					Allergic reactions (urticaria, rhinitis, dyspnoea, Quincke's oedema), anaphylactic shock	
Psychiatric disorders						Nervousness[2], restlessness[2], irritability[2]

System Organ Class	Very common	Common	Uncommon	Rare	Very rare	Not known
Nervous system disorders		Dizziness, headache	Tremor, sweating	Seizures[3] Tension		
Cardiac disorders		¨Ventricular tachycardia[1]	¨Arrhythmia[1] Bradycardia[1]		¨Fibrillation[1] ¨cardiac arrest[1]	
Vascular disorders		¨Hypotension ¨hypertension[1]				
Respiratory, thoracic and mediastinal disorders				Pulmonary oedema		Runny nose and sneezing[2], yawning[3]
Gastrointestinal disorders	Nausea	Vomiting	Diarrhoea[2], dry mouth			
Skin and subcutaneous tissue disorders					Erythema multiforme One case of erythema multiforme cleared promptly after naloxone was discontinued.	Piloerection[2]
Musculoskeletal and connective tissue disorders						Weakness[2], shivering[2],
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)			Death when reversal of opioid depression is abrupt
Investigations						Increased blood pressure when reversal of opioid depression is abrupt

[1] when used in the abrupt reversal of opioid depression (**see Special Warnings**)
[2] 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**)
[3]Seizures have occurred rarely following administration of naloxone; however, a causal relationship to the drug has not been established.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 24 mg/70 kg did not demonstrate toxicity.

In another study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m^2/min) of naloxone followed immediately by 2 mg/kg/h 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 0.2 mg of naloxone (2.2 mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulfate. Paediatric reports include a 2½ year old child who inadvertently received a dose of 20 mg 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 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
Mechanism of action and pharmacodynamics effects

Mechanism of action
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. 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 and if it is given in higher doses it rapidly reverses the effect of morphine and other opioids. If naloxone is given intravenously its onset of action is most rapid to produce an immediate effect and is only slightly slower after intramuscular injection, occurring after approximately 2 minutes. Response to naloxone was 94% if given intramuscularly and 90% if given intravenously, although the difference was not significant. Subcutaneous injection is both slower to accomplish and to exert an effect and intramuscular injection appears as the most frequent route for use in the non-medical setting in published studies. Prenoxad is intended for intramuscular administration.

Clinical efficacy
In a clinical study patients (N=9) with narcotic opioid overdosage recovered consciousness immediately after intravenous injection of 0.4 – 1.2 mg of naloxone given in divided doses over 3 minutes. There was an increase in respiratory rate and volume accompanied by a rise in systolic blood-pressure and dilation of the pupils.

5.2 Pharmacokinetic properties

Absorption
Naloxone is rapidly absorbed following oral administration but high pre-systemic metabolism makes this route unreliable. In healthy volunteers (n=6) intramuscular naloxone showed a relative bioavailability of 35% compared to the intravenous route.
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. 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.
Biotransformation
When naloxone reaches the liver it undergoes extensive biotransformation, almost none of the drug excreted being unchanged. Naloxone is metabolized in the liver, primarily by glucuronide conjugation, with naloxone-3-glucoronide as the major metabolite.
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 plasma half-life is 1-2 hours.

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 was weakly positive in the Ames mutagenicity and in vitro human lymphocyte chromosome aberration tests and 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 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 naloxone should not be mixed with preparations containing bisulfite, metabisulfite, long-chain anions with high molecular weight or alkaline solutions.

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 2 ml prefilled syringe (glass Type I) with a plunger stopper (chlorobutyl). The pack contains two 23G x 1¼" needles.
Keep the syringe in the plastic box in order to protect from light.

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

Ethypharm
194 Bureaux de la Colline - Bâtiment D
92213 Saint-Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0549/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th June 2016
Date of last renewal: 6th June 2021

10 DATE OF REVISION OF THE TEXT

September 2022