Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naloxone Hydrochloride 400 micrograms/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule of solution contains naloxone hydrochloride dihydrate equivalent to 400 micrograms (0.4 mg) naloxone hydrochloride.

Excipient with known effect
Each 1 ml of solution contains 3.55 mg sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the reversal of opioid depression, including respiratory depression, caused by natural or synthetic opioids, the agonist-antagonists nalbuphine and pentazocine, or dextropropoxyphene. Naloxone may also be used for the diagnosis of suspected opioid overdosage. Naloxone may be used to reverse respiratory and other CNS depression in the neonate, resulting from administration of narcotic analgesics to the mother during labour.

4.2 Posology and method of administration

Posology
Opioid overdosage (known or suspected).

Adults
An initial dose of 400 to 2000 micrograms (0.4 mg to 2 mg) of naloxone may be given intravenously and may, if required, be repeated at 2 to 3 minute intervals. The diagnosis of opioid-related toxicity should be reconsidered if there is still failure to respond after a total of 10 mg of naloxone has been administered. If intravenous administration is impracticable, naloxone may be administered by the intramuscular or subcutaneous route.

The duration of action of some opioids (including dextropropoxyphene, dihydrocodeine and methadone) may exceed that of naloxone. In these circumstances, an intravenous infusion of naloxone will provide sustained antagonism of the opioid and obviate the need for repeated injections. Naloxone may be diluted for intravenous infusion in 0.9% (normal) saline or 5% dextrose in water or saline. Addition of 2 mg of naloxone to 500 ml of one of these solutions provided a concentration of 4 micrograms/ml (0.004 mg/ml). Mixtures should be used within 24 hours and any unused solution should be discarded after this time. The rate of infusion should be titrated according to the patients response.

Post operative use: Dosage is individually titrated to maintain adequate analgesia while gaining optimum respiratory response. The usual intravenous dose is 100 to 200 micrograms (0.1 to 0.2 mg) i.e. approximately 1.5 to 3 micrograms (0.0015 to 0.003mg) per kg bodyweight with a two minute interval between each 100 microgram (0.1mg) increment administered.

Depending on the type of opioid, the dose and the time interval from its last administration, repeat doses of naloxone may be required within one to two hours and may be administered by intramuscular injection or by intravenous infusion in order to produce a more sustained effect.

Paediatric population
The usual initial dose is 10 microgram (0.01 mg) per kg of body weight, intravenously. If adequate response does not occur a dose of 100 micrograms (0.1 mg) per kg body weight may be administered. Alternatively, naloxone may be administered by intravenous infusion, if appropriate or if the I.V. route is not feasible, it may be given I.M. or S.C. in divided doses.

Neonatal Use: For opioid-induced depression, the usual initial dose is 10 micrograms (0.01mg) per kg body weight, I.V., I.M. or S.C.
This dose may be repeated, if required at 2 to 3 minute intervals. Alternatively, a single dose of 200 micrograms (0.2 mg) i.e. approximately 60 micrograms (0.06 mg) per kg bodyweight may be administered intramuscularly at birth although the onset of action is slower after I.M. injection. An adequate airway should be established prior to administering naloxone to the apnoeic infant.

Method of administration
Naloxone is for intravenous, intramuscular or subcutaneous injection. It may also be administered by intravenous infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

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Naloxone must be given with caution to patients who have received large doses of opioids or are physically dependent on opioids. Too rapid reversal of opioid effects can cause an acute 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 hydrochloride must be closely monitored. The effect of opioids can be longer than the effect of naloxone hydrochloride and new injections may be necessary.

Naloxone hydrochloride is not effective in central depression caused by agents other than opioids. Reversal of buprenorphine-induced respiratory depression may be incomplete and accordingly, a continuous infusion of naloxone may be appropriate when treating buprenorphine induced respiratory depression. If an incomplete response occurs respiration should be mechanically assisted.

Following the use of opioids during surgery, excessive dosage of naloxone hydrochloride should be avoided, because it may cause excitement, increase in blood pressure and clinically important, reversal of analgesia. A reversal of opioid effects achieved too rapidly may induce nausea, vomiting, sweating or tachycardia.

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.

Naloxone hydrochloride has been reported to induce hypotension, hypertension, ventricular tachycardia, fibrillation and pulmonary oedema. These adverse effects have been observed postoperatively most often 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 administering Naloxone 400 micrograms/ml 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, digoxin). See section 4.8.

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 has 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 3.55 mg sodium per ml, equivalent to 0.18% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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:
For Naloxone hydrochloride insufficient clinical data on exposed pregnancies are available. 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. Naloxone hydrochloride can cause withdrawal symptoms in new-born infants (see section 4.4).

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

Fertility
No clinical data are available. Refer section 5.3 Preclinical safety data for more detail.

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 not to drive, to operate machinery or to 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 the 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 HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In view of the indication and the broad therapeutic margin, overdose is not to be expected. Single doses of 10 mg naloxone hydrochloride i.v. have been tolerated without any adverse effects or changes in laboratory values. Higher than recommended dosage in postoperative use can lead to the return of pain and tension.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidotes, ATC Code: V03AB15

Mechanism of action
Naloxone hydrochloride, a semi synthetic morphine derivative (N-allyl-nor-oxymorphone), is a specific opioid antagonist that acts competitively at opioid receptors. It reveals very high affinity for the opioid receptor sites and therefore displaces both opioid agonists and partial antagonists, such as pentazocine, for example, but also nalorphine. Naloxone hydrochloride does not counteract central depression caused by hypnotics or other non-opioids and does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. Even high doses of the drug (10 times the usual therapeutic dose) produce insignificant analgesia, only slight drowsiness, and no respiratory depression, psychotomimetic effects, circulatory changes, or miosis. In the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity. Because naloxone hydrochloride, unlike nalorphine, does not exacerbate the respiratory depression caused by other substances, it can therefore also be used for differential diagnosis.

Naloxone hydrochloride has not been shown to produce tolerance or cause physical or mental dependence.

In case of opioid dependence, administration of naloxone hydrochloride will enhance the symptoms of physical dependence. When administered intravenously, the pharmacological effect of naloxone hydrochloride will usually be visible within two minutes. The duration of the antagonistic effect depends on dose, but in general is in the range of 1-4 hours. The need for repeated doses depends on the quantity, type and route of administration of the opioid to be antagonised.

5.2 Pharmacokinetic properties

Absorption
Naloxone hydrochloride is rapidly absorbed from the gastrointestinal tract but it is subject to considerable first-pass metabolism and is rapidly inactivated following oral administration. 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
Following parenteral administration, naloxone hydrochloride is rapidly distributed into body tissues and fluids, especially into the brain, because the drug is highly lipophilic. 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 %. Naloxone hydrochloride readily crosses the placenta; however, it is not known whether naloxone hydrochloride is distributed into breast milk.

Biotransformation
Naloxone hydrochloride is rapidly metabolised in the liver, mainly by conjugation with glucuronic acid, and excreted in urine.

Elimination
Naloxone hydrochloride has a short plasma half-life of approximately 1-1.5 hours after parenteral administration. The plasma half-life for neonates is approximately 3 hours. 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 vivorat 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

6.2 Incompatibilities

Naloxone should not be mixed with preparations containing bisulphite, metabisulphite, long chain or high molecular weight anions or any solution having an alkaline pH.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

As packaged for sale: 4 years
Diluted solutions should be used within 24 hours and any unused solution should be discarded after this time.

6.4 Special precautions for storage

Do not store above 25°C. Keep the ampoules in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear glass one-point-cut (OPC) ampoules.
Pack sizes: 3 x 1 ml; 5 x 1 ml and 10 x 1 ml ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.
Naloxone may be diluted for intravenous infusion in 0.9% (normal) saline or 5% dextrose in water or saline. Addition of 2 mg of naloxone to 500 ml of one of these solutions provides a concentration of 4 micrograms/ml (0.004 mg/ml).
Diluted solutions should be used within 24 hours. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road
Citywest Business Park
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0073/111/002

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October 2023,Grace O'Dwyer