Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naloxone Hydrochloride Minijet 400 micrograms/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 400 micrograms naloxone hydrochloride as naloxone hydrochloride dihydrate.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection (injection)
A clear, colourless, solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Naloxone is indicated for the treatment of respiratory depression induced by natural and synthetic opioids, such as codeine, diamorphine, levorphanol, methadone, morphine, concentrated opium alkaloid hydrochlorides and propoxyphene. It is also useful for the treatment of respiratory depression caused by opioid agonist/antagonists nalbuphine and pentazocine. Naloxone is also used for the diagnosis of suspected acute opioid overdose.

4.2 Posology and method of administration

Naloxone hydrochloride may be administered by IV, IM or SC injection or IV infusion.

Adults:
Naloxone may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of naloxone in 500 ml of either solution provides a concentration of 4 micrograms/ml. Infusion should be commenced as soon as practicable after preparation of the mixture in order to reduce microbiological hazards. Preparations not used within 24 hours should be discarded.

The rate of administration should be titrated in accordance with the patient's response. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

Naloxone hydrochloride may be used postoperatively to reverse central depression resulting from the use of opioids during surgery. The usual dosage is 100 - 200 micrograms IV given at 2 to 3 minute intervals to obtain optimum respiratory response while maintaining adequate analgesia. Additional doses may be necessary at one to two hour intervals depending on the response of the patient and the dosage and duration of action of the opioid administered.

For the treatment of known opioid overdosage or as an aid in the diagnosis of suspected opioid overdosage, the usual initial adult dosage of naloxone hydrochloride is 400 - 2000 micrograms IV, administered at 2 to 3 minute intervals if necessary. If no response is observed after a total of 10 mg of the drug has been administered, the depressive condition may be caused by a drug or disease process not responsive to naloxone. When the IV route cannot be used, the drug may be administered by IM or SC injection.

For respiratory depression caused by mixed agonist/antagonists, such as buprenorphine , a continuous intravenous administration of naloxone at a rate of 4mg/70kg/hour is recommended to prevent the recurrence of respiratory depression.

Children:
The usual initial dose in children is 10 micrograms / kg bodyweight given IV. If the dose does not result in the desired degree of clinical improvement, a subsequent dose of 100 micrograms / kg body weight may be administered. If the IV route of

administration is not available, naloxone may be administered IM or SC in divided doses. If necessary naloxone can be diluted with sterile water for injection.

Opioid - induced depression in neonates resulting from the administration of opioid analgesics to the mother during labour may be reversed by administering naloxone hydrochloride 10 micrograms / kg body weight to the infant by IM, IV or SC injections, repeated at intervals of 2 to 3 minutes if necessary. Alternatively, a single IM dose of about 60 micrograms / kg may be given at birth for a more prolonged action. It should be noted that onset of action is slower following IM injection.

Elderly:
In elderly patients with pre-existing cardiovascular disease or in those receiving potentially cardiotoxic drugs, naloxone should be used with caution since serious adverse cardiovascular effects such as ventricular tachycardia and fibrillation have occurred in postoperative patients following administration of naloxone.

4.3 Contraindications

Naloxone is contraindicated in patients with known hypersensitivity to the drug.

4.4 Special warnings and precautions for use

It should be administered with caution to patients who have received large doses of opioids or to those physically dependent on opioids since too rapid reversal may precipitate an acute withdrawal syndrome in such patients. When naloxone hydrochloride is used in the management of acute opioid overdosage, other resuscitation measures should be readily available. A withdrawal syndrome may also be precipitated in newborn infants of opioid-dependent mothers.

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.

Naloxone should be also used with caution in patients with preexisting cardiovascular disease or in those receiving potentially cardiotoxic drugs, since serious adverse cardiovascular effects such as ventricular tachycardia and fibrillation have occurred in postoperative patients following administration of naloxone.

Naloxone is not effective against respiratory depression caused by non-opioid drugs. Reversal of buprenorphrine-induced respiratory depression may be in complete. If an incomplete response occurs respiration should be mechanically assisted as clinically indicated.

Respiratory depression caused by mixed agonist/antagonists such as buprenorphine may require a continuous intravenous administration (see section 4.2) of naloxone as the most effective way to prevent the recurrence of respiratory depression .

4.5 Interaction with other medicinal products and other forms of interactions

No drug or chemical agent should be added to naloxone unless its effect on the chemical and physical stability of the solution has first been established.

4.6 Fertility, pregnancy and lactation

Reproductive studies in mice and rats using naloxone hydrochloride dosage up to 1000 times the usual human dosage have not revealed evidence of impaired fertility or harm to the foetus. Naloxone rapidly crosses the placental barrier so that some therapeutic effect may be anticipated in the neonate. There are no adequate and controlled studies using the drug in pregnant women. Naloxone hydrochloride should be used only when clearly needed.

Since it is not known whether naloxone hydrochloride is distributed into breast milk, the drug should be used with caution in nursing women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, hyperventilation, increased blood pressure, tremulousness and violent behaviour.

In postoperative patients, larger than necessary dosages of naloxone may result in significant reversal of analgesia and in excitement.

Hypotension, hypertension, ventricular tachycardia and fibrillation, hyperventilation and pulmonary oedema have been associated with the use of naloxone postoperatively. Seizures have occurred on rare occasions following the administration of naloxone.

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 have been no reports of acute overdosage due to naloxone hydrochloride.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: V03 AB15

Naloxone hydrochloride is a semisynthetic (N-allylnoroxymorphine hydrochloride) opioid antagonist which is derived from thebaine. When administered in usual doses to patients who have not recently received opioids, naloxone exerts little or no pharmacologic effect. Even extremely high doses of the drug (10 times the usual therapeutic dose) produces insignificant analgesia, only slight drowsiness and no respiratory depression, psychotomimetic effects, circulatory changes or miosis.

In patients who have received large doses of diamorphine or other analgesic drugs with morphine-like effects, naloxone antagonises most of the effects of the opioid. There is an increase in respiratory rate and minute volume, arterial pCO_2 decreases toward normal and blood pressure returns to normal if depressed. Naloxone antagonises mild respiratory depression caused by small doses of opioids. Because the duration of action of naloxone is generally shorter than that of the opioid, the effects of the opioid may return as the effects of naloxone dissipates. Naloxone antagonises opioid-induced sedation or sleep. Reports are conflicting on whether or not the drug modifies opioid-induced excitement or seizures.

Naloxone does not produce tolerance or physical or psychological dependence. However, 0.4 mg of naloxone hydrochloride administered SC will precipitate potentially severe withdrawal symptoms in patients physically dependent on opioids or pentazocine. The precise mechanism of action of the opioid antagonist effects of naloxone is not known. Naloxone is thought to act as a competitive antagonist at μ (mu), K(kappa) or s(delta) opioid receptors in the central nervous system. It is thought that the drug has the highest affinity for the μ receptor.

5.2 Pharmacokinetic properties

Naloxone has an onset of action within 1 to 2 minutes following IV administration and within 2 to 5 minutes following SC or IM administration. The duration of action depends on the dose and route of administration and is more prolonged following IM administration than after IV administration. In one study, the duration of action was 45 minutes following IV administration of naloxone hydrochloride 0.4 mg/70 kg.

Following parenteral administration, naloxone is rapidly distributed into body tissues and fluids. In rats, high concentrations are observed in the brain, kidney, spleen, lungs, heart and skeletal muscles. In humans, the drug readily crosses the placenta. It is not known whether naloxone is distributed into milk.

The plasma half-life of naloxone has been reported to be 60 to 90 minutes in adults and about 3 hours in neonates.

Naloxone is rapidly metabolised in the liver, principally by conjugation with glucuronic acid. The major metabolite is naloxone-3-glucuronide. Naloxone also undergoes N-dealkylation and reduction of the 6-keto group followed by conjugation. Limited studies with radiolabeled naloxone indicated that 25 - 40% IV doses of the drug is excreted as metabolites in urine in 6 hours, about 50% in 24 hours and 60 - 70% in 72 hours.

5.3 Preclinical safety data

Not applicable since naloxone has been used in clinical practice for many years and its effects in man are well known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Dilute Hydrochloric Acid (for pH adjustment)
Water for Injection

6.2 Incompatibilities

Naloxone should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular anions or any solution having an alkaline pH.

This medicinal product should not be mixed with other medicinial products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 30 months.
Once opened: Use immediately. Discard any unused portion.

Chemical and physical in-use stability has been demonstrated in dextrose 5% w/v and sodium chloride 0.9% w/v solutions for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, the in-use storage conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep the syringe in the outer carton to protect from light.
For storage of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container

The solution is contained in a borosilicateType I glass syringe with a polystyrene plunger rod And a bromobutyl compound (FM457/0) plunger stopper.

The 1 mL syringe has a luer lock connector with a plastic rigid tip cap.

The 2 mL syringe has a 1 1/4 inch stainless steel needle with an elastomer needle shield.

One syringe per carton.

Not all pack sizes may be marketed.

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

When given by infusion, naloxone hydrochloride injection may be diluted with normal saline (0.9% w/v), or 5% w/v dextrose solutions.
Any unused product or waste material should be disposed of in accordance with local requirements.
Naloxone hydrochloride injection must be free from particles and discolouration prior to use.

7 MARKETING AUTHORISATION HOLDER

DLRC Pharma Services Limited
Chesterfield House
Clonmannon
Ashford
Wicklow
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22684/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 April 1988

Date of last renewal: 18 April 2008

10 DATE OF REVISION OF THE TEXT

May 2019