SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Naloxone Medo 0.4mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 1ml contains 0.4mg of naloxone hydrochloride (as naloxone hydrochloride dihydrate).

Excipient(s) with known effect: 1 ml of solution for injection/infusion contains 3.38 mg (0.15mmol) of sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion
Clear, colourless or almost colourless solution.
pH: 3.0 – 4.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Complete or partial reversal of CNS and especially respiratory depression, caused by natural or synthetic opioids.
- Diagnosis of suspected acute opioid overdose or intoxication.
- Complete or partial reversal of respiratory and other CNS depression in the neonate whose mothers have received opioids.

4.2 Posology and method of administration

Posology

Complete or partial reversal of CNS and especially respiratory depression, caused by natural or synthetic opioids
Adults
Dosage is determined for each patient in order to obtain optimum respiratory response while maintaining adequate analgesia. An i.v. injection of 0.1 to 0.2 mg naloxone hydrochloride (approx. 1.5-3 µg/kg) is usually sufficient. If necessary, additional i.v. injections of 0.1 mg can be administered at 2 minute intervals until satisfactory respiration and consciousness are obtained. An additional injection can again be necessary within 1 to 2 hours, depending on the type of active substance to be antagonised (short-term effect or slow release), the amount administered and time and mode of administration. Naloxone can alternatively be administered as an i.v. infusion.

Infusion:
The duration of action for some opioids is longer than that of the naloxone hydrochloride i.v. bolus. Therefore, in situations where depression is known to be induced by such substances or there is a reason to suspect this, naloxone hydrochloride should be administered as a continuous infusion. The infusion rate is determined according to the individual patient, depending on the response of the patient to the i.v. bolus and on the reaction of the patient to the i.v. infusion. The use of the continuous intravenous infusion should be carefully considered and respiratory assistance should be applied if necessary.

Children
Initially, 0.01-0.02 mg naloxone hydrochloride per kg i.v. at intervals of 2-3 minutes until satisfactory respiration and consciousness are obtained. Additional doses may be necessary at 1- to 2-hours intervals depending on the response of the patient and the dosage and duration of action of the opiate administered.

Diagnosis of suspected acute opioid overdose or intoxication
Adults
The initial dose is usually 0.4-2 mg naloxone hydrochloride i.v. If the desired improvement in the respiratory depression is not obtained immediately after i.v. administration, the injections can be repeated at intervals of 2-3 minutes.
Naloxone hydrochloride can also be injected intramuscularly (initial dose usually 0.4-2 mg) if intravenous administration is not possible. If 10 mg naloxone hydrochloride does not produce a significant improvement, this suggests that the depression is wholly or partially caused by other pathological conditions or active substances other than opioids.

Children
The usual starting dose is 0.01 mg naloxone hydrochloride per kg i.v. If the satisfactory clinical response is not achieved, an additional 0.1 mg/kg injection can be administered. Depending on the individual patient, an i.v. infusion may also be necessary. If i.v. administration is not possible, naloxone hydrochloride can also be injected i.m. (initial dose 0.01 mg/kg), divided into several doses.

Reversal of respiratory and other CNS depression in the neonate whose mothers have received opioids
The usual dosage is 0.01 mg naloxone hydrochloride per kg i.v. If the respiratory function is not reversed to a satisfactory level with this dosage, the injection can be repeated at 2 to 3 minute intervals. If i.v. administration is not possible, naloxone hydrochloride can also be injected i.m. (initial dose 0.01 mg/kg).

Elderly
In elderly patients with pre-existing cardiovascular disease or in those receiving potentially cardiotoxic drugs, naloxone hydrochloride 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 hydrochloride.

Method of administration
The medicinal product can be injected intravenously (i.v.) or intramuscularly (i.m.) or can be given via intravenous infusion.

The i.m. administration of naloxone hydrochloride should only be used in cases where an i.v. administration is not possible.

The most rapid effect is obtained by means of i.v. administration, which is why this method of administration is recommended in acute cases.

When naloxone is administered i.m., it is necessary to remember that the onset of action is slower than following i.v. injection. However, i.m. administration has a longer action than i.v. administration.
The onset of action varies from a half to two minutes after i.v. administration, to three minutes after i.m. administration.
The duration of action by i.v. is approximately 20 to 30 minutes. By i.m.., it is 2 hours 30 minutes to 3 hours.
It has to be considered that necessary i.m. dosages are generally higher than i.v. dosages and that dosage has to be adapted to the individual patient.

As it is possible that the duration of effect of some opioids (e.g. dextropropoxyphene, dihydrocodeine, methadone) is longer than that of naloxone hydrochloride, the patients must be kept under continuous supervision, and repeated doses must be given if necessary.

For incompatibilities and instructions on dilution of the medicinal product before administration, see section 6.2 and 6.6, respectively.

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

Naloxone hydrochloride must be given with caution to patients who have received high doses of opioids or are physically dependent on opioids. Too rapid reversal of the opioid effect can cause an acute withdrawal syndrome in such patients. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest have been described. This also applies to newborn 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. 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.

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 hydrochloride 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per 1ml, 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. However, there is an increased risk of respiratory depression which can be fatal in case of overdose.

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.

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 take part in road traffic, 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, < 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).

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.

Chills, agitation and anxiety have sometimes been reported.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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 and pharmacodynamic effects
Naloxone hydrochloride, a semisynthetic morphine derivative (N-allyl-noroxymorphone), 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.
The diffusion of naloxone at the cerebral level is good: at the maximum serum concentrations (i.e. 15 minutes after injection), the cerebral concentrations are one and a half times higher than the plasma concentrations.
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.
After i.v. injection, naloxone undergoes rapid degradation: only small quantities of non-metabolized naloxone are found in plasma.
The degradation of naloxone takes place according to an enterohepatic cycle: dealkylation with reduction of group 6 keto and glycuroconjugation give rise to different metabolites including, in particular, 2-naloxone-glycuronide.

Elimination
Naloxone hydrochloride has a short plasma half-life of approximately 45-90 minutes after parenteral administration. The plasma half-life for neonates is approximately 3 hours.
The total body clearance amounts to 22 ml/min/kg.
The elimination of naloxone and its metabolites is urinary (70% in 72 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 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
Disodium edetate
Hydrochloric acid
Water for injection

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf-life after first opening
After first opening the medicinal product should be used immediately.

Shelf-life after dilution
Chemical and physical in-use stability has been demonstrated for 30 hours at 25°C.
From a microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25°C.
Keep the ampoules in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Clear glass ampoules in moulded PVC trays, sealed with a PE foil and packed in a carton box.
Packs of 10 ampoules of 1ml solution are available.

6.6 Special precautions for disposal and other handling

For i.v. infusion naloxone hydrochloride is diluted with sodium chloride 0.9% or glucose 5%. 5 ampoules of naloxone hydrochloride (2 mg) per 500 ml give 4µg/ml.
This medicinal product is for single use only.

Please inspect the medicinal product visually prior to use (also after dilution). Use only clear and colourless solutions practically free from particles.

7. MARKETING AUTHORISATION HOLDER

A.L.Medi-Market, 3 Hakatif street, Emek Hefer Industrial Park, 3877701

8. MARKETING AUTHORISATION NUMBER(S)

177-34-37511-99

9. MANUFACTURER

Medochemie Ltd., 1-10 Constantinoupoleos street, 3011, Limassol, Cyprus

Approved in September 2024