SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nalotas Solution for Injection/Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

Naloxone hydrochloride dihydrate.

Each ml of solution for injection contains 400 micrograms naloxone hydrochloride (as naloxone hydrochloride dihydrate).

Excipient with known effect

1 ml solution for injection/infusion contains 3.54 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.

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 IV injection of 0.1 mg to 0.2 mg naloxone hydrochloride (approximately 1.5–3 micrograms/kg) is usually sufficient. If necessary, additional IV 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 400 micrograms/ml can alternatively be administered as an IV infusion.

Infusion

The duration of action for some opioids is longer than that of the naloxone hydrochloride IV 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 IV bolus and on the reaction of the patient to the IV 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 IV at intervals of 2–3 minutes until satisfactory respiration and consciousness are obtained. Additional doses may be necessary at 1 to 2-hour intervals depending on the response of the patient and the dosage and duration of action of the opiate administered.

Diagnosis and treatment of suspected acute opioid overdose or intoxication

Adults

The initial dose is usually 0.4–2 mg naloxone hydrochloride IV. If the desired improvement in the respiratory depression is not obtained immediately after IV administration, the injections can be repeated at intervals of 2–3 minutes.

If intravenous administration is not possible, Naloxone 400 micrograms/ml can also be injected intramuscularly (initial dose usually 0.4–2 mg).

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 IV. If the satisfactory clinical response is not achieved, the dose can be increased in the next injection to 0.1 mg/kg. Depending on the individual patient, an IV infusion may also be necessary.

If IV administration is not possible, Naloxone 400 micrograms/ml can also be injected IM (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 IV. 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 IV administration is not possible, Naloxone 400 micrograms/ml can also be injected IM (initial dose 0.01 mg/kg).

Elderly

In elderly patients with pre-existing cardiovascular disease or in those receiving potentially cardiotoxic drugs, Naloxone 400 micrograms/ml 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 (IV) or intramuscularly (IM) or can be given via intravenous infusion.

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

The IM administration of Naloxone 400 micrograms/ml should only be used in cases where an IV administration is not possible.

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

When Naloxone 400 micrograms/ml is administered IM, it is necessary to remember that the onset of action is slower than following IV injection; however, IM administration has a longer action than IV administration. The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride, varying between 45 minutes and 4 hours.

Furthermore, it has to be considered that necessary IM dosages are generally higher than IV 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.

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 400 micrograms/ml 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 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. 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 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.

This medicinal product contains 3.54 mg sodium per ml, equivalent to 0.2% 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).

Breastfeeding

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 not drive or operate machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Adverse reactions reported in the following table by MedDRA System Organ Class (SOC), Preferred Term and frequency. The following frequency categories are 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).

System Organ Class	Frequency	Undesirable effects
Immune System Disorders	Very rare	Allergic reactions (urticaria, rhinitis, dyspnoea, Quincke's oedema), anaphylactic shock.
Nervous system disorders	Common	Dizziness, headache.
Nervous system disorders	Uncommon	Tremor, sweating.
Nervous system disorders	Rare	Seizures, tension[1].
Cardiac Disorders	Common	Tachycardia.
Cardiac Disorders	Uncommon	Arrhythmia, bradycardia.
Cardiac Disorders	Very rare	Fibrillation, cardiac arrest.
Vascular Disorders	Common	Hypotension, hypertension[2].
Respiratory, Thoracic and Mediastinal Disorders	Very rare	Pulmonary oedema[3].
Gastrointestinal disorders	Very common	Nausea[4].
Gastrointestinal disorders	Common	Vomiting.
Gastrointestinal disorders	Uncommon	Diarrhoea, dry mouth.
Skin and Subcutaneous Tissue Disorders	Very rare	Erythema multiforme[5].
General Disorders and Administration Site Condition	Common	Postoperative pain.
General Disorders and Administration Site Condition	Uncommon	Hyperventilation, irritation of vessel wall (after IV administration); local irritation and

		inflammation (after IM administration).

1. 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.

2. 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.

3. Pulmonary oedema has also occurred with the postoperative use of naloxone hydrochloride.

4. 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 antagonization of the opioid effect.

5. One case of erythema multiforme cleared promptly after naloxone hydrochloride was discontinued.

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 https://pv.pharmacyboardkenya.org

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 IV 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

Naloxone hydrochloride, a semisynthetic 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

Non-clinical data revealed no 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 (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

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

24 months.

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 24 hours below 25°C. From the 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°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C. Keep the ampoules in the outer carton to protect from light. Do not use if particulate matter is present.

6.5 Nature and contents of container

Clear glass ampoules, glass type I, Ph. Eur.

Pack sizes: 5 × 1 ml and 10 × 1 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For IV infusion Naloxone 400 micrograms/ml is diluted with sodium chloride 0.9% or glucose 5%.

Diluting 5 ampoules of Naloxone 400 micrograms/ml (2 mg) per 500 ml gives 4 micrograms/ml solution.

For single use only. Discard any unused contents.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation Holder

Tasa Pharma Limited

Unit C1-C3

Kay complex

Nairobi

Kenya

Manufacturing site address

Tasa Pharma Limited

Unit C1-C3

Kay complex

Nairobi

Kenya

8. MARKETING AUTHORIZATION NUMBER

H2022/CTD10130/23039

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

2023 September 26

10. DATE OF REVISION OF THE TEXT

2023 September 26