Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naloxone Hydrochloride Accord 400 micrograms/ml solution for injection/infusion in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml pre-filled syringe contains 400 micrograms naloxone hydrochloride (as dihydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion in pre-filled syringe.
Clear and colourless solution, practically free from particles, pH 3.1 to 4.5 and osmolality 250 to 350 mOsmol/kg.

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.

Naloxone Hydrochloride Accord is indicated in adults, adolescents, children and infants weighing more than 4 kg.

4.2 Posology and method of administration

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

Naloxone Hydrochloride Accord should only be administered by a healthcare professional.

For incompatibilities and instructions on dilution of the product before administration, see sections 6.2 and 6.6. The i.m. administration of Naloxone Hydrochloride Accord 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 Hydrochloride Accord 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 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 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.

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 100 to 200 micrograms naloxone hydrochloride (approx. 1.5-3 micrograms/kg) is usually sufficient. If necessary, additional i.v. injections of 100 micrograms 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 Hydrochloride Accord 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.

Paediatric population:
Initially, 10-20 micrograms 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.

Naloxone Hydrochloride Accord pre-filled syringe should not be used in infants weighing less than 4 kg.

Diagnosis of suspected acute opioid overdose or intoxication

Adults:
The initial dose is usually 400 micrograms-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 Accord can also be injected intramuscularly (initial dose usually 400 micrograms-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.

Paediatric population:
The usual starting dose is 10 micrograms naloxone hydrochloride per kg i.v. If the satisfactory clinical response is not achieved, an additional 100 micrograms/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 Accord can also be injected i.m. (initial dose 10 micrograms/kg), divided into several doses.

Naloxone Hydrochloride Accord pre-filled syringe should not be used in infants weighing less than 4 kg.

Reversal of respiratory and other CNS depression in the neonate whose mothers have received opioids

The usual dosage is 10 micrograms 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 Accord can also be injected i.m. (initial dose 10 micrograms/kg).

Elderly:
In elderly patients with pre-existing cardiovascular disease or in those receiving potentially cardiotoxic drugs, Naloxone Hydrochloride Accord 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Naloxone Hydrochloride Accord 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 Accord 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 medicine contains less than 1 mmol sodium (23 mg) per 1 ml (400 micrograms) dose, that is to say 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.

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 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 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 and pharmacodynamic effects
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

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
Hydrochloric acid, concentrated (for pH adjustment)
Water for injections

6.2 Incompatibilities

It is recommended that naloxone should not be mixed with preparations containing bisulphite, metabisulphite, long-chain anions with high-molecular-weight or alkaline solutions.

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

6.3 Shelf life

Unopened syringe
2 years

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 36 hours at 2 to 8 °C and at 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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep the syringe in the twist box in order to protect from light.

6.5 Nature and contents of container

1 ml clear glass pre-filled syringe with tip cap, plunger stopper (grey bromobutyl rubber stopper) and plunger rod (polypropylene). Graduations per 0.1 mL are present on the barrel of the syringe.

The pre-filled syringe is supplied with needle (23 G; 30 mm), packaged in an outer box (Twist box).

Pack sizes: one pre-filled syringe and one needle.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only. Discard any unused solution immediately after use. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For i.v. infusion Naloxone Hydrochloride Accord is diluted with sodium chloride 9 mg/ml (0.9%) solution or glucose 50 mg/ml (5%) solution. 5 pre-filled syringes of Naloxone Hydrochloride Accord (2 mg) per 500 ml give concentration of 4 micrograms/ml.

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Limited
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8 MARKETING AUTHORISATION NUMBER

PA2315/254/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th June 2023

10 DATE OF REVISION OF THE TEXT