Summary of the Product Characteristics

hameln

Naloxone-hameln 0.4 mg/ml Injection

DESCRIPTION

Before dilution:
Clear and colourless solution

pH: 3.1-4.5

Osmolality: 270-310 mOsMol/kg

After dilution:
Clear and colourless solutions practically free from particles (please refer to "Warning & Precaution" section for type of reconstitution solution).

CONTENTS

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

PROPERTIES

Pharmacotherapeutic group: Antidotes

ATC-Code: V03AB15

Naloxone hydrochloride, a semisynthetic morphine derivative (N-allylnor-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.

Naloxone has an onset of action within 1 to 2 minutes following intravenous administration and within 2 to 5 minutes following subcutaneous or intramuscular administration. The duration of action depends on the dose and route of administration and is more prolonged following intramuscular administration than after intravenous administration. The duration of action is reported to be up to several hours but the practical duration is probably 1 hour or less. Repeat doses of naloxone may be required depending on the amount, type and route of administration of the opioid being antagonised, as well as the duration of action of naloxone. Following parenteral administration, naloxone is rapidly distributed into body tissues and fluids. It is rapidly metabolised in the liver, principally by conjugation with glucuronic acid, and is excreted in the urine. Naloxone is 50% protein-bound. The mean plasma half-life of naloxone has been reported to be about 60 minutes in adults with a range of from about 30 to 80 minutes, and about 3 hours in neonates.

INDICATIONS

Naloxone is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids including propoxyphene, methadone, codeine, morphine and heroin, and the mixed opioid agonist-antagonist analgesics such as pentazocine. Naloxone is also indicated for the diagnosis of suspected acute opioid overdosage.

RECOMMENDED DOSAGE

General

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 HCl 0.4 mg/ml 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 HCl 0.4 mg/ml 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 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 HCl 0.4 mg/ml 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 HCl 0.4 mg/ml 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 Naloxone-hameln 0.4 mg/ml Injection not possible, Naloxone HCl 0.4 mg/ml 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 HCl 0.4 mg/ml 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 HCl 0.4 mg/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.

CONTRAINDICATIONS

Naloxone HCl 0.4 mg/ml is contraindicated in patients with hypersensitivity to naloxone hydrochloride or to any of the excipients of this medicinal product.

WARNINGS & PRECAUTIONS

Naloxone HCl 0.4 mg/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 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 pul-

monary 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 HCl 0.4 mg/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).

This medicinal product contains 3.8 mmol (88.5 mg) sodium per maximum daily dose of 10 mg naloxone hydrochloride. This should be taken into consideration by patients on a controlled sodium diet.

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.

Incompatibilities

It is recommended that infusions of naloxone hydrochloride should not be mixed with preparations containing bisulphite, metabisulphite, longchain or high-molecular-weight anions, or solutions with an alkaline pH.

This medicinal product must not be mixed with other medicinal products except with sodium chloride 0.9% or glucose 5%. 5 ampoules of Naloxone HCl 0.4 mg/ml (2 mg) per 500 ml give 4 µg/ml.

Special precautions for disposal and other handling

For i.v. infusion Naloxone HCl 0.4 mg/ml is diluted with sodium chloride 0.9% or glucose 5%. 5 ampoules of Naloxone HCl 0.4 mg/ml (2 mg) per 500 ml give 4 µg/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.

INTERACTION WITH OTHER MEDICAMENTS

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.

PREGNANCY & LACTATION

Pregnancy

For Naloxone hydrochloride insufficient clinical data on exposed pregnancies are available. Animal studies have shown reproductive. 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.

Lactation

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.

ADVERSE REACTIONS

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.

SYMPTOMS & TREATMENTS OF OVERDOSAGE

Symptoms

Symptoms of overdosage would be expected to be similar to the effects seen with therapeutic use (see Adverse Reactions).

Treatment

Treatment of overdosage is symptomatic and supportive.

STORAGE CONDITIONS & PHARMACEUTICALS PRECAUTIONS

Keep the ampoules in the outer carton in order to protect from light.

Do not store above 30°C.

Do not freeze.

Store diluted solutions below 25°C.

Keep out of the reach and sight of children!

Jauhi daripada kanak-kanak!

SHELF LIFE

Please refer to outer label.

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

Packing sizes:

Type I clear, colourless glass ampoules.

Packs of 5 ampoules of 1 ml.
Packs of 10 ampoules of 1 ml.

Not all pack sizes may be marketed.

MANUFACTURED BY:

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