Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naloxone 400 microgram/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 1 ml solution for injection or infusion contains 400 microgram naloxone hydrochloride (as naloxone hydrochloride dihydrate)
Excipient: 1 ml contains 3.54 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion

Clear and colourless solution
pH = 3.0 – 4.0
osmolality= 0.3 Osmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Complete or partial reversal of CNS depressive effects, especially respiratory depression, caused by natural or synthetic opioids and partial agonist/antagonist opioids.
Diagnosis of suspected acute opioid overdose or intoxication.

4.2 Posology and method of administration

Method of Administration
The medicinal product can be injected intravenously (i.v.), intramuscularly (i.m.) 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 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 hydrochloride 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 action of some opioids is longer than that of naloxone hydrochloride, the patient must be constantly monitored and repeated doses must be administered, if necessary.

Posology
Completeor partialreversal of CNSdepressive effects,especiallyrespiratorydepression,caused by natural or syntheticopioids and partialagonist/antagonistopioids.

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 microgram naloxone hydrochloride is usually sufficient. If necessary, additional i.v. injections of 100 microgram can be administered at 2 - 3 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.

Naloxone400 microgram/ml can alternatively be administered as an i.v. infusion, if the duration of action for some opioids is longer than that of the naloxone hydrochloride i.v. bolus.
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 (see section 6.6).

Childrenandadolescents

Initially, 10-20 microgram 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.
The dose in children and adolescents can be different due to local recommendations.

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.

Diagnosis and treatment of suspectedacuteopioid overdoseor intoxication

Adults
The usual starting dose for adults is 400-2000 microgram naloxone hydrochloride, administered intravenously. If the desired degree of reversal and improvement of the respiratory function are not attained directly after the i.v. injection, the injection can be repeated intravenously at 2-3 minute intervals. Naloxone hydrochloride can also be injected intramuscularly, if i.v. 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 than opioids.

Children and adolescents
The usual starting dose is 10 microgram naloxone hydrochloride/kg body weight i.v. If a satisfactory clinical response is not achieved, an increased additional dose of 100 microgram/kg can be administered. Depending on the individual patient, an i.v. infusion may be necessary. If i.v. administration is not possible, Naloxone 400 microgram/ml can also be injected i.m. (initial dose 10 microgram/kg), divided into several doses.
The dose in children and adolescents can be different due to local recommendations.

Neonateswhosemothershave receivedopioids

The usual dosage is 10 microgram 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, Naloxone400 microgram/ml can also be injected i.m. (initial dose 10 microgram/kg).
The dose in neonates can be different due to local recommendations.

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 microgram/ml should be given with caution to patients,who have received high doses of opioids or are physically dependent on opioides (including neonates born to women who are opioid dependent). In such cases a prompt and complete reversal of opioid effects by a too high dose of Naloxone may precipitate acute withdrawal symptoms. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest have been described. This also applies to newborn infants of such patients.

Patients who have responded satisfactorily to naloxone hydrochloride treatment must be carefully monitored. The effect of opioids can be longer than the effect of naloxone hydrochloride and new injections may be necessary.

Too large doses of naloxone hydrochloride in post-operative patients may result in a clear reversal in analgesia, excitement and an elevation in blood pressure. A reversal of opioid effects achieved too rapidly may induce nausea, vomiting, sweating or tachycardia.

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.

Naloxone should be used with caution in patients with pre-existing cardiovascular disease or in patients who are taking relatively cardiotoxic drugs (e.g. calcium channel blockers, beta-blockers, digoxin). (see section 4.8)

This medicine contains less than 1 mmol sodium (23 mg) per ampoule (1ml), that is to say essentially 'sodium-free'. Each ampoule of 1 ml solution contains 3.54 mg sodium.

4.5 Interaction with other medicinal products and other forms of interactions

The effect of naloxone is based on the interaction with opioids and opioid agonists. At the usual naloxone dose there is no interaction with barbiturates and tranquillizers. Data on the interaction with alcohol are not uniform. In patients with multiple intoxication with opioids and sedatives or alcohol, the result of naloxone administration may be delayed, dependent on the cause of intoxication.

In administration of naloxone to patients that had buprenorphine as analgesic, complete analgesia can be restored. It is assumed that this effect is caused by the arched form of the dose-response curve of buprenorphine with decreasing analgesia at (too) high doses. However, reversal of respiratory depression caused by buprenorphine is limited.

In administration of naloxone in coma caused by clonidine-overdosing, serious hypertension has been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data available on the use of naloxone hydrochloride in pregnant women.
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 the new-born infant (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

No studies on the effects on the ability to drive and use machines have been performed.

Patients who have received naloxone hydrochloride to reverse the effect 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 exertation for at least 24 hours, since the effect of the opioids may return.

4.8 Undesirable effects

The following undesirable effects are ranked according to system organ class and to their frequency:
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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)

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, 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

Regarding the indication and the wide therapeutic index, overdosing is not to be expected.

Single doses of 10 mg naloxone hydrochloride intravenously and cumulative doses up to 90 mg/day subcutaneously have been tolerated without undesirable effects or changes in laboratory parameters.

Thus far no cases of intoxication are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidotes
ATC code: V03AB15

Naloxone hydrochloride 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.

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 dependance. 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 2 minutes.

The duration of the antagonistic effect depends on the dose, but in general is in the range of 45 minutes to 4 hours.

The need of repeated doses depends on the quantity, type and route of administration of the opioid that must be antagonized.

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 (the bioavailability is about 1/50 compared to parenteral administration). 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. At maximal serum concentration (15 minutes after injection) the cerebral concentration is 1.5 times higher than the plasma concentration.
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 de-alkylation with reduction of the 6-ketogroup. Naloxone hydrochloride and its metabolites are excreted into urine (70 % in 72 hours).

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, diluted (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Naloxone is incompatible with formulations containing bisulphite, metabisulphite, “long-chain” or high molecular weight anions. Also incompatible with alkaline solutions.

6.3 Shelf life

3 years

Shelf-life after first opening:
The medicinal product must be used immediately.

Shelf-life after dilution:
From a microbiological point of view, the product 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 reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Type I clear, colourless glass ampoules.
One pack contains 10 ampoules of 1 ml.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only. Discard any unused solution.
Please inspect the medicinal product visually prior to use.
Use only clear and colourless solutions free from particles.

For i.v. infusion Naloxone 400 microgram/ml Solution for Injection is diluted with sodium chloride 0.9% w/v or glucose 5% w/v. 5 ampoules of Naloxone 400 microgram/ml Solution for Injection (2 mg) diluted to 500 ml give a final concentration of 4 microgram/ml.

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

7 MARKETING AUTHORISATION HOLDER

Orpha-Devel Handels und Vertriebs GmbH
Wintergasse 85/1B
A-3002 Purkersdorf
Austria

8 MARKETING AUTHORISATION NUMBER

PA1353/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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