NALOXONE HYDROCHLORIDE INJECTION USP

1. NAME OF THE MEDICINAL PRODUCT
NALOXONE HYDROCHLORIDE INJECTION USP 0.4 mg - 1 mL, solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ampoule of 1 mL contains 400 micrograms (0.4 mg) naloxone hydrochloride (as naloxone hydrochloride dihydrate).
Excipient with known effect: Each ampoule of 1 mL contains 3.5 mg of sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection or infusion.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Naloxone may be used for the complete or partial reversal of opioid depression, including mild to severe respiratory depression induced by natural and synthetic opioids, the agonist/antagonists nalbuphine and pentazocine, or dextropropoxyphene. It may also be used for the diagnosis of suspected acute opioid overdosage. Naloxone may be used to counteract respiratory and other CNS depression in the newborn resulting from the administration of analgesics to the mother during childbirth

4.2 Posology and method of administration
NALOXONE HYDROCHLORIDE INJECTION USP is for intravenous (IV), intramuscular (IM) or subcutaneous (SC) injection. It may also be administered by intravenous infusion.

Intravenous infusion:
Addition of 2 mg of naloxone hydrochloride to 500 mL of normal saline (0.9%) or to 500 mL of 5% dextrose in water or in saline will provide a concentration of 4 micrograms/mL (0.004 mg/mL). After 24 hours, any unused solution should be discarded. The rate of infusion should be titrated according to the patient's response to the infused naloxone hydrochloride and to any previously administered bolus doses.
Naloxone hydrochloride should not be mixed with preparations containing bisulphite, metabisulphite, long-chain or high molecular weight anions or any solution having an alkaline pH. No drug or chemical agent should be added to naloxone hydrochloride unless its effect on the chemical and physical stability of the solution has first been established. Before administration, parenteral drugs should be inspected visually for particulate matter and discolouration whenever the solution and container permit.

Adults:
Opioid overdosage (known or suspected):
An initial dose of 400 to 2,000 micrograms (0.4 mg to 2 mg) of naloxone hydrochloride may be given intravenously and may, if required, be repeated at 2 to 3 minute intervals. The diagnosis of opioid-related toxicity should be reconsidered if there is still failure to respond after a total of 10 mg of naloxone has been administered. If intravenous administration is impracticable, naloxone may be administered by the intramuscular or subcutaneous route. The duration of action of some opioids (including dextropropoxyphene, dihydrocodeine and methadone) may exceed that of naloxone hydrochloride. In these circumstances an intravenous infusion of naloxone hydrochloride will provide sustained antagonism of the opioid and obviate the need for repeated injections.

Post-operative use:
When Naloxone Hydrochloride Injection is used postoperatively, the dose should be titrated for each patient in order to obtain optimum respiratory response while maintaining adequate analgesia.

Intravenous doses of 100 to 200 micrograms (0.1 to 0.2 mg), corresponding to 1.5 to 3 micrograms (0.0015 to 0.003 mg) per kg body weight, may be used. The dose should be titrated according to the individual patient's response and a full 2 minutes should be allowed between each 100 micrograms (0.1 mg) increment of naloxone hydrochloride administered. Depending on the type of opioid, the dose and the time interval from its last administration, repeat doses of naloxone hydrochloride may be required within one to two hours and may be administered by intramuscular injection or by intravenous infusion in order to produce a more sustained effect.

Children:
The usual initial dose is 10 micrograms (0.01 mg) per kg body weight, intravenously. A subsequent dose of 100 micrograms (0.1 mg) per kg body weight may be used if required.
Naloxone hydrochloride may be administered by intravenous infusion, if appropriate. Alternatively, it may be given IM or SC in divided doses.

Neonatal use:
For opioid-related depression, the usual initial dose is 10 micrograms (0.01 mg) per kg body weight, IV, IM or SC, and this may be repeated, if required, at 2 to 3 minute intervals. Alternatively, a single dose of 200 micrograms (0.2 mg), approximately 60 micrograms (0.06 mg) per kg body weight, may be administered intramuscularly at birth. An adequate airway should be established prior to administering naloxone hydrochloride to the apnoeic infant.

4.3 Contraindications
Naloxone hydrochloride should not be given to patients who are known to be hypersensitive to the drug or any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use
NALOXONE HYDROCHLORIDE INJECTION USP must be given with caution to patients who have received large doses of opioids or are physically dependent on opioids. Too rapid reversal of opioid effects 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 opioid. 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.

The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include but are not limited to the following: body aches, diarrhoea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea, vomiting, nervousness, restlessness, irritability, shivering, trembling, abdominal cramps, weakness and increased blood pressure. In the neonate, opioid withdrawal may also include: convulsions, excessive crying and hyperactive reflexes.

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 INJECTION USP 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.

In addition to naloxone hydrochloride, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage and vasopressor agents should be available and employed when necessary to counteract acute poisoning.

Renal insufficiency/failure: The safety and effectiveness of naloxone hydrochloride in patients with renal insufficiency/failure have not been established in clinical trials. Caution should be exercised and patients monitored when naloxone hydrochloride is administered to this patient population.

Liver disease: The safety and effectiveness of naloxone hydrochloride in patients with liver disease have not been established in well-controlled clinical trials. In one small study in patients with liver cirrhosis, plasma naloxone concentrations were approximately six times higher than in patients without liver disease.

Naloxone administration had a diuretic effect in these patients with cirrhosis. Caution should be exercised when naloxone hydrochloride is administered to a patient with liver disease.

This medicine contains less than 1 mmol sodium (23 mg) per ampoule of 1 mL, 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).

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.

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 to avoid road traffic, operate machinery or 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 IV administration); local irritation and inflammation (after IM administration).
Higher than recommended dosage in postoperative use can lead to the return of pain. A fast reversal of opioid effect can induce hyperventilation.

4.9 Overdose

In view of the indication and the broad therapeutic margin overdose is not expected. Single dose of 10 mg naloxone hydrochloride IV have been tolerated without any adverse effects or changes in laboratory values. Higher than the recommended dosage in postoperative use can lead to the return of pain and tension.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidote 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.

Metabolism

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, water for injections, dilute hydrochloric acid.

6.2 Incompatibilities

Naloxone hydrochloride should not be mixed with preparations containing bisulphite, metabisulphite, long-chain or high molecular weight anions or any solution having an alkaline pH. No drug or chemical agent should be added to naloxone hydrochloride unless its effect on the chemical and physical stability of the solution has first been established

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25 °C. Protect from light.

6.5 Nature and contents of container

Box of 10 ampoules of 1 mL or box of 100 ampoules of 1 mL.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

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PANPHARMA