**Approved Professional Information for Naloxone HCl Fresenius**

**SCHEDULING STATUS** S4

## 1. NAME OF THE MEDICINE

**NALOXONE HCl 0,4 mg/1 ml FRESENIUS** solution for injection

**NALOXONE HCl NEONATAL 0,02 mg/1 ml FRESENIUS** solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NALOXONE HCl 0,4 mg/1 ml FRESENIUS: Each 1 ml ampoule contains 0,4 mg naloxone hydrochloride.

NALOXONE HCl NEONATAL 0,02 mg/1 ml FRESENIUS: Each 2 ml ampoule contains 0,04 mg naloxone hydrochloride.

**Excipients with known effect**

Each 1 ml solution contains 3,48 mg of sodium.

For the full list of excipients, see section 6.1.

Sugar free.

## 3. PHARMACEUTICAL FORM

Clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Opioid-induced respiratory depression.

Neonatal respiratory depression secondary to the administration of opioids to the mother.

## 4.2 Posology and method of administration

**Posology**

**(i) Adults:**

***Opioid toxicity:***

0,4 to 2 mg intravenously, repeated, if necessary, at two-to-three-minute intervals, as needed. If no response has been observed after a total dose of 10 mg, then the diagnosis of overdosage with medicines other than opioids should be considered.

***Post-operative opioid depression:***

0,1 to 0,2 mg intravenously at intervals of at least 2 minutes to obtain an optimum respiratory response while maintaining adequate analgesia.

**(ii) Paediatrics:**

***Neonates – Opioid-induced depression:***

(resulting from the administration of opioid analgesics to the mother during labour)
0,01 mg/kg body mass of the infant by intramuscular, intravenous or subcutaneous injection, repeated at two-to-three-minute intervals if necessary. Alternatively, a single intramuscular dose of 0,06 mg/kg body mass may be given at birth for a more prolonged action.

***Children – Opioid toxicity:***

0,01 mg/kg body mass intravenously, followed, if necessary, by a larger dose of 0,1 mg/kg body mass.
All patients receiving NALOXONE HCl FRESENIUS should be closely observed as the duration of action of some opioids exceeds that of naloxone hydrochloride and repeated doses

may be required.

**Method of administration**

NALOXONE HCl FRESENIUS may be administered subcutaneously, intramuscularly, or intravenously. In emergency situations intravenous administration is recommended. Suitable diluents for intravenous administration are sterile solutions containing sodium chloride or dextrose.

## 4.3 Contraindications

Hypersensitivity to naloxone hydrochloride or any of the excipients of NALOXONE HCl FRESENIUS listed in section 6.1.

## 4.4 Special warnings and precautions for use

NALOXONE HCl FRESENIUS should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

The signs and symptoms of opioid withdrawal in patients 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 and vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In the neonate, opioid withdrawal may also include convulsions, excessive crying and hyperactive reflexes.

Patients who respond satisfactorily to NALOXONE HCl FRESENIUS–must be closely monitored and repeated doses of NALOXONE HCl FRESENIUS should be administered as necessary, since the duration of action of some opioids may exceed that of NALOXONE HCl FRESENIUS. Large doses of NALOXONE HCl FRESENIUS 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 HCl FRESENIUS is not effective against respiratory depression due to non-opioid medicines.

Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs, respiration should be mechanically assisted.

In addition to NALOXONE HCl FRESENIUS, other resuscitative measures, such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor medicines should be available and employed when necessary to counteract acute opioid poisoning.

Abrupt post-operative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary oedema and cardiac arrest which may result in death.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary oedema and cardiac arrest have been reported in post-operative patients following

administration of naloxone hydrochloride, as in NALOXONE HCl FRESENIUS. Coma and encephalopathy have been reported as sequelae of these events. These have occurred in post-operative patients most of whom had pre-existing cardiovascular disorders or received other medicines which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, NALOXONE HCl FRESENIUS should be used with caution in patients with pre-existing cardiac disease or patients who have received medicines with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation and pulmonary oedema. It has been suggested that the pathogenesis of pulmonary oedema associated with the use of NALOXONE HCl FRESENIUS is similar to neurogenic pulmonary oedema, i.e., a centrally mediated massive catecholamine response, leading to a dramatic shift of blood volume into the pulmonary vascular bed, resulting in increased hydrostatic pressures.

NALOXONE HCl FRESENIUS should also be used with caution in patients with pre-existing pulmonary disease, since sudden exacerbation of underlying pulmonary disease may occur.

**Use in hepatic impairment**

The safety and effectiveness of NALOXONE HCl FRESENIUS in patients with liver disease have not been established. Caution should be exercised when NALOXONE HCl FRESENIUS is administered to patients with hepatic disease.

**Use in renal impairment**

The safety and effectiveness of NALOXONE HCl FRESENIUS in patients with renal insufficiency/failure have not been established. Caution should be exercised when NALOXONE HCl FRESENIUS is administered to this patient population.

**Paediatric population**

See section 4.2 **Posology and method of administration – Paediatrics**.

NALOXONE HCl FRESENIUS contains less than 1 mmol sodium (23 mg) per ampoule (1 ml), that is to say essentially sodium free.
Each 1 ml solution contains 3,48 mg sodium.

## 4.5 Interaction with other medicines and other forms of interaction

The effect of NALOXONE HCl FRESENIUS is based on the interaction with opioids and opioid agonists, reversing effects of opioids; rapid reversal may precipitate acute withdrawal syndrome in opioid dependence. At the usual NALOXONE HCl FRESENIUS dose, there is no interaction with barbiturates and tranquillisers. Data on the interaction with alcohol are not uniform. In patients with multiple intoxication with opioids and sedatives or alcohol, the result of NALOXONE HCl FRESENIUS administration may be delayed, dependent on the cause of intoxication.

Complete analgesia can be restored following administration of NALOXONE HCl FRESENIUS to patients that had buprenorphine as analgesic. 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.

Serious hypertension has been reported following administration of naloxone hydrochloride, as in NALOXONE HCl FRESENIUS, to patients in a coma caused by clonidine-overdosing.

NALOXONE HCl FRESENIUS reverses the analgesic and other effects of opioid

agonist/antagonists such as pentazocine, so may precipitate withdrawal symptoms if used concurrently with these medicines in physically dependent patients.

NALOXONE HCl FRESENIUS reverses the analgesic and other effects of opioid agonist analgesics and may precipitate withdrawal symptoms if used concurrently with these medicines in physically dependent patients, including patients receiving methadone to treat opioid dependence.

When NALOXONE HCl FRESENIUS is used post-operatively to reverse the central depressive effects of opioid agonists used as anaesthesia adjuncts, the dose of NALOXONE HCl FRESENIUS must be carefully titrated to achieve the desired effect without interfering with control of post-operative pain or causing other adverse effects.

## 4.6 Pregnancy and lactation

### Pregnancy

Safety in pregnancy has not been established.

Caution should be taken when administering it to neonates of mothers who are physically dependent on opioids as a withdrawal syndrome may be precipitated.

### Breastfeeding

Safety during lactation has not been established.

It is not known whether NALOXONE HCl FRESENIUS is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when NALOXONE HCl FRESENIUS is administered to a nursing woman.

## 4.7 Effects on ability to drive and use machines

NALOXONE HCl FRESENIUS may cause dizziness (see section 4.8).

Patients who have received NALOXONE HCl FRESENIUS to reverse the effects of opioids should be warned not to drive a vehicle or 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

**Immune system disorders:**

*Less frequent:* Allergic reactions (urticaria, rhinitis, dyspnoea, Quincke's oedema), anaphylactic shock.

**Nervous system disorders:**

*Frequent:* Dizziness, headache.

*Less frequent:* Tremor, seizures, sweating, tension.

**Cardiac disorders:**

*Frequent:* Tachycardia.

*Less frequent:* Dysrhythmias, bradycardia.

**Vascular disorders:**

*Frequent:* Hypotension, hypertension.

**Respiratory, thoracic and mediastinal disorders:**

*Less frequent:* Pulmonary oedema.

**Gastrointestinal disorders:**

*Frequent:* Nausea, vomiting.

*Less frequent:* Diarrhoea, dry mouth.

**Skin and subcutaneous tissue disorders:**

*Less frequent:* Erythema multiforme.

**General disorders and administration site conditions:**

*Frequent:* Post-operative pain.

*Less frequent:* Hyperventilation, irritation of vessel wall (after IV administration).

*Post-operative.* The following adverse events have been associated with the use of NALOXONE HCl FRESENIUS in post-operative patients: hypotension, ventricular tachycardia or fibrillation, dyspnoea, pulmonary oedema and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Adverse cardiovascular effects have occurred most frequently in post-operative patients with a pre-existing cardiovascular disease or in those receiving other medicines that produce similar adverse cardiovascular effects.

Excessive doses of NALOXONE HCl FRESENIUS in post-operative patients may result in significant reversal of analgesia and may cause agitation (see sections 4.2 and 4.4).

Nausea and vomiting have been reported in post-operative 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.

Higher than recommended dosage in post-operative use can lead to the return of pain. A fast reversal of opioid effect can induce hyperventilation.

*Opioid depression*. Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary oedema and cardiac arrest, which may result in death (see section 4.4).

*Opioid dependence* (see section 4.4). Agitation and paraesthesias have been reported less frequently with the use of NALOXONE HCl FRESENIUS.

*Drug abuse and dependence.* NALOXONE HCl FRESENIUS is an opioid antagonist.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of NALOXONE HCl FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of NALOXONE HCl FRESENIUS. Health care providers are asked to report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Health care providers are asked to report any suspected Adverse Drug Reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius- kabi.com, and to the relevant medicine's regulatory authority in the country where the product is marketed.

### 4.9 Overdose

See section 4.8.

Treatment is symptomatic and supportive.

## 5. PHARMACOLOGICAL PROPERTIES

**Category and class:** A 1.4 Respiratory stimulants.

**Pharmacotherapeutic group:** Antidotes, ATC code: V03AB15.

### 5.1 Pharmacodynamic properties

Naloxone hydrochloride is a competitive antagonist at opioid receptors. The duration of the antagonistic effects of naloxone hydrochloride is from 1 to 4 hours depending on dose.

In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.

Naloxone hydrochloride prevents or reverses the effects of opioids, including respiratory depression, sedation and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist/antagonists such as pentazocine.

Naloxone hydrochloride is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. Naloxone hydrochloride does not produce respiratory depression, psychotomimetic effects of pupillary

constriction. In the absence of opioid or agonistic effects of other opioid antagonists it exhibits essentially no pharmacological activity.

Naloxone hydrochloride has not been shown to produce tolerance or to cause physical or psychological dependence. In the presence of physical dependence on opioids, naloxone hydrochloride will produce withdrawal symptoms.

While the mechanism of action of naloxone hydrochloride is not fully understood, the prevalence of evidence suggests that naloxone hydrochloride antagonises the opioid effects by competing for the same receptor sites.

## 5.2 Pharmacokinetic properties

### Absorption

When naloxone hydrochloride is administered intravenously, the onset of action is generally apparent within two minutes. The onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride. Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of naloxone hydrochloride, however, will also be dependent upon the amount, type and route of administration of the opioid being antagonised.

### Distribution

Following parenteral administration, naloxone hydrochloride is rapidly distributed in the body.

### Biotransformation

Naloxone hydrochloride is metabolised in the liver, primarily by conjugation with glucuronic acid.

**Elimination**

Naloxone hydrochloride has a plasma half-life of about one hour.

Naloxone hydrochloride is excreted in the urine. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3,1 ± 0,5 hours.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Methylparaben 0,17 % *m/v* (as preservative)

Glacial acetic acid (for pH-adjustment)

Sodium acetate trihydrate

Sodium chloride

Water for injection.

### 6.2 Incompatibilities

NALOXONE HCl FRESENIUS should not be mixed with preparations containing sulphite, metabisulphite, long chain or high molecular mass anions, or any solution having an alkaline pH.

No medicine or chemical should be added to NALOXONE HCl FRESENIUS unless its effect on the chemical and physical stability of the solution has first been established.

### 6.3 Shelf life

60 months.

### 6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

### 6.5 Nature and contents of container

NALOXONE HCl 0,4 mg/1 ml FRESENIUS: 1 ml OPC type I amber glass ampoules packed in boxes of 10.

NALOXONE HCl NEONATAL 0,02 mg/1 ml FRESENIUS: 2 ml OPC type I amber glass ampoules packed in boxes of 10.

### 6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

## 7. HOLDER OF CERTIFICATES OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten 6020

Gqeberha

South Africa

## 8. REGISTRATION NUMBERS

NALOXONE HCl 0,4 mg/1 ml FRESENIUS: 27/1.4/0157

NALOXONE HCl NEONATAL 0,02 mg/1 ml FRESENIUS: 27/1.4/0158

## 9. DATE OF FIRST AUTHORISATION

25 November 1993

## 10. DATE OF REVISION OF THE TEXT

24 January 2023.