# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. Name of the medicinal product

Nubin Injection

## 2. Qualitative and quantitative composition

**Each ml contains:** Nalbuphine Hydrochloride ..... 10 mg

1 ampoule of 2 ml contains 20 mg nalbuphine hydrochloride.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

NUBIN 10 mg/ml solution for injection is indicated for the short-term relief of moderate to severe pain. It can also be used for pre- and postoperative analgesia.

### 4.2 Posology and method of administration

Adults

The usual recommended dose for adults is 10 - 20 mg for patients with 70 kg body weight, which is equivalent to 0.1 – 0.3 mg/kg body weight. This dose may be administered intravenously, intramuscularly or subcutaneously and may be repeated after 3 to 6 hours, if necessary. The maximum single dose in adults must not exceed 20 mg. The posology must be adapted to the intensity of pain and the physical status of the patient.

Children and adolescents

The usual recommended dose for children is 0,1 - 0,2 mg/kg body weight. This dose may be administered intravenously, intramuscularly or subcutaneously. Intramuscular as well as subcutaneous administration might be painful and should be avoided in children.

The dose may be repeated after 3 to 6 hours, if necessary. The single maximum dose is fixed with 0,2 mg nalbuphine hydrochloride per kilogram body weight.

There are no adequate data for the treatment of children younger than 1.5 years.

Elderly people

Due to increased bioavailability and decreased systemic clearance it is suggested to start with the lowest dose of nalbuphine hydrochloride.

Patients with hepatic / renal impairment

Patients with moderate and mild renal impairment may show an abnormal reaction upon standard dosages. Therefore, the product should be used with caution in these patients.

Nalbuphine hydrochloride is contraindicated in patients with hepatic disorders and severe renal impairment .

NUBIN 10 mg/ml solution for injection is not suitable for long term treatment.

**4.3 Contraindications**

- hypersensitivity to the active substance or to any of the excipients
- severe renal impairment
- hepatic impairment
- concomitant treatment with μ-agonistic opioids e.g. morphine and fentanyl

**4.4 Special warnings and precautions for use**

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially `sodium-free´.

Opioid dependence

NUBIN 10 mg/ml solution for injection may not be used as a substitute for heroin, methadone or other opioids in dependent persons. In these cases the withdrawal symptoms may be considerably intensified.

Withdrawal symptoms, including increased pain, can occur in patients with chronic pain treated with other μ-agonistic opioids e.g. morphine and fentanyl.

Abuse of NUBIN 10 mg/ml solution for injection can lead to psychological and physical dependence. Special attention is required before treating emotionally unbalanced patients or patients with opioid-misuse in their medical history.

Head injury and increased intracranial pressure

It is possible that potent analgesics may increase intracranial pressure and so cause respiratory depression. In case of head injury, inner head injury or already existing increased intracranial pressure this effect might be intensified. In addition, potent analgesics can cause effects that may mask the course of the disease in patients with head injury. Therefore, NUBIN 10 mg/ml solution for injection must only be used if really necessary and with the utmost caution.

Renal and hepatic disorders

As NUBIN 10 mg/ml solution for injection is metabolised in the liver and eliminated renally, nalbuphine hydrochloride is contraindicated in patients with hepatic disorders and severe renal impairment (see section 4.3). Patients with moderate and mild renal impairment may show abnormal reactions upon standard dosages. Caution is required in these patients.

Obstetric use (see section 4.6)

Foetal and neonatal adverse effects reported following the administration of nalbuphine hydrochloride to the mother during labour include foetal bradycardia, respiratory depression at birth, apnoea, cyanosis, and hypotension. Some of these events have been life-threatening. Maternal administration of naloxone during labour has reversed these effects in some cases. Nalbuphine hydrochloride should only be used during labour and delivery if clearly indicated and if the potential benefit outweighs the risk to the infant. Newborns should be monitored for respiratory depression, apnoea, bradycardia and arrhythmias if Nalbuphine hydrochloride has been used.

Precautions

10 mg NUBIN 10 mg/ml solution for injection causes respiratory depression comparable to that caused by 10 mg morphine. Unlike morphine, there is a ceiling effect to the respiratory depressant effect of nalbuphine.

There is a ceiling for respiratory depression at a dose of approximately 30 mg, and an analgetic ceiling at approximately 50 mg administered during a short period. Patients with pain conditions who have a high opioid requirement should be offered an opioid with no analgetic ceiling.

Respiratory depression raised by NUBIN 10 mg/ml solution for injection may be treated with naloxone hydrochloride, if necessary. NUBIN 10 mg/ml solution for injection must be administered with great caution and in very small dosages to patients who suffer from impaired respiration (e.g. caused by other medical treatment, uremia, bronchial asthma, serious infections, cyanose or respiratory obstruction).
Nalbuphine hydrochloride should be used with caution in patients with heart insufficiency, paralytic ileus, biliary colic, epilepsy and hypothyroidism.
During administration, antagonist treatment should be available (naloxone).

**4.5 Interaction with other medicinal products and other forms of interaction**

Contra-indicated combinations

+ Pure morphine agonists (such as morphine, pethidine, dextromoramide, dihydrocodeine, dextropropoxyphene, methadone, levacethylmethadol):
Pure μ-agonists reduce analgesic effect due to competitive receptor blockage.

Non recommended combinations:

+ Alcohol:
Alcohol potentiates the sedative effect of morphine-based analgesics.
Alcoholic beverages and medicinal products containing alcohol must be avoided.

Precautions

+ Other central nervous system suppressants, such as other morphine derivatives (analgesics and antitussives), sedative antidepressants, sedative H1 antihistamines, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances:
These substances may cause an increased risk of respiratory depression, potentially life threatening in case of overdose.
There is no information available regarding the potential for pharmacokinetic interactions between nalbuphine and other medicinal products. Caution is recommended when nalbuphine is combined with potent enzyme inhibitors or medicinal products with a narrow therapeutic range.

**4.6 Pregnancy and lactation**

Usage during pregnancy

There are inadequate data regarding the use of nalbuphine hydrochloride in pregnant

women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk in humans is unknown. Pregnant women should only be treated with nalbuphine hydrochloride if the anticipated benefit to the mother exceeds the possible risk to the foetus.

As with all opioids, chronic use by the mother, particularly at the end of pregnancy may produce a withdrawal syndrome in the newborn, regardless of the dose.

As is the case with every opioid nalbuphine hydrochloride has not been studied in terms of efficacy and safety in premature labour or delivery.

When nalbuphine hydrochloride is administered to the mother directly before or during delivery, newborns should be monitored for respiratory depression, apnoea, bradycardia and arrhythmias (see section 4.4 and 4.8).

Usage during lactation

Nalbuphine hydrochloride is excreted in breast-milk. Lactation should be discontinued for 24 hours after treatment with NUBIN 10 mg/ml solution for injection.

### 4.7 Effects on ability to drive and use machines

NUBIN 10 mg/ml solution for injection reduces the ability to respond and has therefore a major influence on the ability to drive and use machines. These activities have to be avoided until the effects of nalbuphine hydrochloride have subsided.

### 4.8 Undesirable effects

The following undesirable effects are ranked according to system organ class and to their frequency:

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)

Nervous system disorders:

Very common: Sedation

Common: Perspiration, Drowsiness, Vertigo, Dry mouth, Headache

Rare: Light numbness in the head, Nervousness, Tremor, Withdrawal symptoms,

Paresthesia

Very rare: Euphoria

Psychiatric disorders:

Common: Dysphoria

Very rare: Hallucination, Confusion, personality disorder trait

Respiratory, thoracic and mediastinal disorders:

Rare: Respiratory difficulties

Cardiac disorders:

Very rare: Bradycardia, Tachycardia, Lung oedema

Vascular disorders:

Very rare: Hypotension, Hypertension

Eye disorders:

Very rare: Watery eyes, Blurred vision

Immune system disorders:

Very rare: Allergic reaction

General disorders and administration site conditions:

Very rare: Pain in the puncture, Flushing

Skin and subcutaneous tissue disorders:

Very rare: Urticaria

Gastrointestinal disorders:

Common: Vomiting, Nausea

Pregnancy, puerperium and perinatal conditions:

Very rare: respiratory depression in newborn children, retarded circulation in newborn children

NUBIN 10 mg/ml solution for injection can cause certain withdrawal symptoms if used in patients who exert opioids in an excessive way.

When NUBIN 10 mg/ml solution for injection is used during delivery it can raise respiratory depression and/or retarded circulation in newborn children with deleterious consequences. In these cases naloxone hydrochloride must be kept available as an antidote.

**4.9 Overdose**

Administration of high doses of nalbuphine hydrochloride (intramuscular or intravenous) produces several symptoms of overdose - like respiratory depression, sedation, sleepiness, unconsciousness and light uncomfortableness.
Naloxone hydrochloride can be used as a specific antidote to nalbuphine hydrochloride. However, primary attention should be given to respiratory and cardiovascular function. Symptomatic and supportive therapy is mostly sufficient for slight and moderate overdosage. Oxygen, plasma volume expanders and other auxiliaries may be used, if necessary.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids, Morphinane derivatives
ATC code: N02AF02
Nalbuphine hydrochloride is an opioid with kappa-agonistic and mu-antagonistic properties. Beside the essential agonistic (analgesic) effect nalbuphine hydrochloride has antagonistic effects of about a fourth of nalorfine and ten times of pentazocine. Nalbuphine hydrochloride has minimal abuse potential and has no effect on the digestive and urinary smooth muscles. Nalbuphine hydrochloride minimally delays gastric emptying and intestinal transit. It does not induce difficulty in micturition.

### 5.2 Pharmacokinetic properties

-In adults, the effect takes place 2 to 3 minutes after intravenous administration and less than 15 minutes after intramuscular or subcutaneous injection.
The duration of action ranges from 3 to 6 hours.The half-life period is 2,93 ± 0,795 hours.
-In children of 1.5 years of age and above, the effect takes place 2 to 3 minutes after intravenous injection and 20 to 30 minutes after intramuscular or subcutaneous injection. The duration of action ranges from 3 to 4 hours.
The protein binding of nalbuphine is moderate (about 50%)."
-Nalbuphine hydrochloride is metabolised in the liver.
There are seven metabolites that are already isolated. The most important metabolite is N-(hydroxyketocyclobutyl)-methylnornalbuphine, the other metabolites are isomers of the same and correspond to hydroxylated nalbuphine. All metabolites seem to have

no particular effect.

There is no information regarding enzymes catalysing the formation of these metabolites.

-Nalbuphine hydrochloride is excreted in the urine in terms of glucuronide metabolites.

-No studies have been performed in patients with renal impairment or hepatic impairment.

### 5.3 Preclinical safety data

Reproductive toxicity studies with parenterally administered nalbuphine were performed in rats and rabbits. In a pre- and postnatal study in rats, an increase in preand postnatal mortality and a decrease in offspring weight were observed at high doses.

Nalbuphine hydrochloride exerted no effects on fertility in male and female rats. No teratogenic effect was observed in rats and rabbits.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Citric acid, anhydrous

Sodium citrate

Sodium chloride

Hydrochloric acid (for pH adjustment)

Water for injection

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

3 years

The product has to be used immediately after opening.

### 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.

### 6.5 Nature and contents of container

Colourless glass, Type I.

Ampoules of 2 ml, in packages of 10 ampoules.

**6.6 Special precautions for disposal**

For single use only.

Only clear solutions practically free from particles should be used. The solution must be visually inspected prior to use.

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

**Special precautions for disposal and other handling**

Not stated

## 3. Marketing Authorisation Holder:

The Searle Company Limited

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