Summary of Product Characteristics

1. **Name of the Medicinal Product**

NULPHIN Injection (Nalbuphine hydrochloride 10 mg/ml)

2. Quality and Quantitative Composition

Each 1 ml ampoule contains sterile solution of Nalbuphine hydrochloride 10 mg/ml.

3. Pharmaceutical Form

Solution for injection.

4. Clinical Particulars

4.1 Therapeutic indication

NULPHIN Injection is indicated for the relief of moderate to severe pain. NULPHIN Injection can also be used as a supplement to surgical anesthesia, an adjunct to preoperative and postoperative analgesia, and for obstetrical analgesia during labor and delivery.

Pediatrics (< 18 years of age): Because clinical experience in children is limited, the administration of NULPHIN Injection in this age group is not recommended.

4.2 Posology and method of administration

NULPHIN Injection is a sterile solution suitable for subcutaneous, intramuscular, or intravenous injection.

The usual recommended adult dose is 10 mg for a 70 kg individual, administered subcutaneously, intramuscularly or intravenously; this dose may be repeated every 3 to 6 hours as necessary. Dosage should be adjusted according to the severity of the pain, physical status of the patient, and other medications which the patient may be receiving. (See Interaction with Other Central Nervous System Depressants under WARNINGS). In non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg.

The use of NULPHIN Injection as a supplement to balanced anesthesia requires larger doses than those recommended for analgesia. Induction doses of NULPHIN Injection range from 0.3 mg/kg to 3 mg/kg intravenously to be administered over a 10 to 15 minutes period with maintenance doses of 0.25 to 0.5 mg/kg in single intravenous administrations as required. The use of NULPHIN Injection may be followed by respiratory depression which can be reversed with the opioid antagonist NARCAN® (naloxone hydrochloride).

NULPHIN Injection is physically incompatible with nafcillin and ketorolac.

4.3 Contraindication

NULPHIN Injection should not be administered to patients who are hypersensitive to nalbuphine hydrochloride, or to any of the other ingredients in NULPHIN Injection.

4.4 Special warning and precautions for use

WARNINGS

NULPHIN Injection should be administered as a supplement to surgical anesthesia only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

Naloxone, resuscitative and intubation equipment and oxygen should be readily available.

Drug Abuse

Caution should be observed in prescribing NULPHIN Injection for emotionally unstable patients, or for individuals with a history of opioid abuse. Such patients should be closely supervised when long-term therapy is contemplated.

Drug Dependence

In patients physically dependent on opiate drugs, NULPHIN Injection should not be given prior to detoxification since withdrawal symptoms are likely to be produced.

Patients Dependent on Opioids

Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NULPHIN Injection. If necessary, narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until symptomatic relief.

Use in Ambulatory Patients

NULPHIN Injection may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NULPHIN Injection should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

Use in Emergency Procedures

Maintain patient under observation until recovered from NULPHIN Injection effects that would affect driving or other potentially dangerous tasks.

Use in Pregnancy (Other Than Labor)

Safe use of NULPHIN Injection in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should be administered to pregnant women only if clearly needed.

Use During Labor and Delivery

The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to 1:6. Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis, and hypotonia. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage attributed to fetal bradycardia has occurred. A sinusoidal fetal heart rate pattern associated with the use of nalbuphine has also been reported. NULPHIN Injection should be used with caution in women during labor and delivery, and newborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if NULPHIN Injection has been used.

Head Injury and Increased Intracranial Pressure

The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NULPHIN Injection should be used in these circumstances only when essential, and then should be administered with extreme caution.

Interaction with Other Central Nervous System Depressants

Although NULPHIN Injection possesses opioid antagonist activity, there is evidence that in nondependent patients it will not antagonize an opioid analgesic administered just before, concurrently, or just after an injection of NULPHIN Injection. Therefore, patients receiving an opioid analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NULPHIN Injection may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS

General

Impaired Respiration:

At the usual adult dose of 10 mg/70 kg, NULPHIN Injection causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NULPHIN Injection. Respiratory depression induced by NULPHIN Injection can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NULPHIN Injection should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, remia, bronchial asthma, severe infection, cyanosis, or respiratory obstructions).

Impaired Renal or Hepatic Function:

Because NULPHIN Injection is metabolized in the liver and excreted by the kidneys, NULPHIN Injection should be used with caution in patients with renal or liver dysfunction and administered in reduced amounts.

Myocardial Infarction:

As with all potent analgesics, NULPHIN Injection should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery:

As with all opioid analgesics, NULPHIN Injection should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Cardiovascular System:

During evaluation of NULPHIN Injection in anesthesia, a higher incidence of bradycardia has been reported in patients who did not receive atropine pre-operatively.

Information for Patients

Patients should be advised of the following information:

- NULPHIN Injection is associated with sedation and may impair mental and physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery.
- NULPHIN Injection is to be used as prescribed by a physician. Dose or frequency should not be increased without first consulting with a physician since NULPHIN Injection may cause psychological or physical dependence.
- The use of NULPHIN Injection with other opioids can cause signs and symptoms of withdrawal.
- Abrupt discontinuation of NULPHIN Injection after prolonged usage may cause signs and symptoms of withdrawal.

4.5 Interaction with other medicinal products and other forms of interactions

Although NULPHIN Injection possesses opioid antagonist activity, there is evidence that in nondependent patients it will not antagonize an opioid analgesic administered just before, concurrently, or just after an injection of NULPHIN Injection. Therefore, patients receiving an opioid analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NULPHIN Injection may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

4.6 Pregnancy and lactation

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and in rabbits at dosages as high as approximately 14 and 31 times respectively the maximum recommended daily dose and revealed no evidence of impaired fertility or harm to the fetus due to NULPHIN Injection. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed (see **WARNINGS**).

Non-teratogenic Effects: Neonatal body weight and survival was reduced when NULPHIN Injection was subcutaneously administered to female rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 8-17 times the maximum recommended therapeutic dose. The clinical significance of this effect is unknown.

Use During Labor and Delivery

See WARNINGS.

Nursing Mothers

Limited data suggest that NULPHIN Injection (nalbuphine hydrochloride) is excreted in maternal milk but only in a small amount (less than 1% of the administered dose) and with a clinically insignificant effect. Caution should be exercised when NULPHIN Injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

4.7 Effects on ability to drive and use machine

NULPHIN Injection may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of NULPHIN Injection and know how they will react to the medication [see **PRECAUTIONS; Information for Patients**].

4.8 Undesirable effects

ADVERSE REACTIONS

The most frequent adverse reaction in 1,066 patients treated in clinical studies with NULPHIN Injection was sedation 381 (36%).

Less frequent reactions were: sweaty/clammy 99 (9%), nausea/ vomiting 68 (6%), dizziness/vertigo 58 (5%), dry mouth 44(4%), and headache 27 (3%).

Other adverse reactions which occurred (reported incidence of 1% or less) were:

CNS Effects: Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.

Cardiovascular: Hypertension, hypotension, bradycardia, tachycardia.

Gastrointestinal: Cramps, dyspepsia, bitter taste.

Respiratory: Depression, dyspnea, asthma.

Dermatologic: Itching, burning, urticaria.

Miscellaneous: Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

Allergic Reactions: Anaphylactic/anaphylactoid and other serious hypersensitivity reactions have been reported following the use of nalbuphine and may require immediate, supportive medical treatment. These reactions may include shock, respiratory distress, respiratory arrest, bradycardia, cardiac arrest, hypotension, or laryngeal edema. Other allergic -type reactions reported include stridor, bronchospasm, wheezing, edema, rash, pruritus, nausea, vomiting, diaphoresis, weakness, and shakiness.

Events Observed during Post-marketing Surveillance of Nalbuphine Hydrochloride

Other reports include pulmonary edema, agitation and injection site reactions such as pain, swelling, redness, burning and hot sensations.

Fetal death has been reported where mothers received nalbuphine hydrochloride during labor and delivery.

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

DRUG ABUSE AND DEPENDENCE

NULPHIN Injection have been shown to have a low abuse potential. When compared with drugs which are not mixed agonist-antagonists. It has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Drug abuse has been reported infrequently. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine (See **WARNINGS**).

Care should be taken to avoid increases in dosage or frequency of administration which in susceptible Individuals might result in physical dependence.

Abrupt discontinuation of NULPHIN Injection following prolonged use has been followed by symptoms of opioid withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.

4.9 Overdose

The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

The administration of single doses of 72 mg of NULPHIN Injection subcutaneously to 8 normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

NULPHIN Injection is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis. Receptor studies show that NULPHIN Injection binds to mu, kappa, and delta receptors, but not to sigma receptors. NULPHIN Injection is primarily a kappa agonist/partial mu antagonist analgesic.

The onset of action of NULPHIN Injection occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours, and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The opioid antagonist activity of NULPHIN Injection is one-fourth as potent as nalorphine and 10 times that of pentazocine.

NULPHIN Injection may produce the same degree of respiratory depression as equi analgesic doses of morphine. However, NULPHIN Injection exhibits a ceiling effect such that increases in doses greater than 30mg do not produce further respiratory depression.

NULPHIN Injection by itself has potent opioid antagonist activity at doses equal to or lower than its analgesic dose. When administered following or concurrent with mu agonist opioid analgesics (e.g., morphine, oxymorphone, fentanyl), NULPHIN Injection may partially reverse or block opioid-induced respiratory depression from the mu agonist analgesic. NULPHIN Injection may precipitate withdrawal in patients dependent on opioid drugs. NULPHIN Injection should be used with caution in patients who have been receiving mu opioid analgesics on a regular basis.

5.2 Pharmacokinetic properties

The onset of action of NULPHIN Injection occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours, and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The metabolic pathway for nalbuphine has not been defined, but is likely hepatic.

5.3 Preclinical Safety data

Laboratory Tests

NULPHIN Injection may interfere with enzymatic methods for the detection of opioids depending on the specificity/sensitivity of the test. Consult the test manufacturer for specific details.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found in a 24 months carcinogenicity study in rats and an 18 months carcinogenicity study in mice at oral doses as high as the equivalent of approximately three times the maximum recommended therapeutic dose.

No evidence of a mutagenic/genotoxic potential to NULPHIN Injection was found in the Ames. Chinese Hamster Ovary HGPRT, and Sister Chromatid Exchange, mouse micronucleus, and rat bone marrow cytogenicity assays. NULPHIN Injection induced an increased frequency of mutation in mouse lymphoma cells.

6. Pharmaceutical Particulars

6.1 List of excipients

Anhydrous citric acid, Sodium chloride, Sodium citrate dihydrate, Hydrochloride acid, Water for injection.

6.2 Incompatibilities

NULPHIN Injection is physically incompatible with nafcillin and keterolac.

6.3 Shelf life

24 months (2 years).

6.4 Special precautions for storage

Store at 30°C (86°F). Protect from excessive light. Store in carton until contents have been used.

6.5 Nature and contents of container

NULPHIN INJECTION injection for intramuscular, subcutaneous or intravenous use is a sterile solution available in 1ml ampoule contain 10mg of nalbuphine hydrochloride per ml.

10 ampoules are packed in a carton together with a partition of ampoule, and a package insert.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. Marketing Authorization Holder

American Taiwan Biopharm Co., Ltd.

No. 1, Eastwater Building, 16th Floor, Soi Vibhavadi-Rangsit 5, Vibhavadi-Rangsit Road, Chom Phon, Chatuchak, Bangkok, 10900

8. Marketing Authorization Numbers

1C xxxxx/62

9. Date of authorization

Xxxx

10. Date of revision of the text

16 January 2020