Summary Report of Benefit-Risk Assessment

NALDEBAIN EXTENDED RELEASE INJECTION 75 MG/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Dinalbuphine sebacate
Product Registrant	Intega Pte Ltd
Product Registration Number	SIN16058P
Application Route	Abridged evaluation
Date of Approval	15 December 2020

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A INTRODUCTION

Naldebain Extended Release Injection 75 mg/ml is indicated for the relief of moderate to severe acute postsurgical pain.

The active substance, dinalbuphine sebacate, is a prodrug comprising two nalbuphine molecules joined by sebacoyl ester. In the systemic circulation, dinalbuphine sebacate is converted to the active moiety, nalbuphine. Nalbuphine is a synthetic narcotic analgesic and is a mixed opioid agonist-antagonist (kappa agonist, partial mu agonist).

Naldebain Extended Release Injection 75 mg/ml is available as an injection containing 75 mg/ml of dinalbuphine sebacate. Other ingredients in the product are benzyl benzoate and sesame oil.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, dinalbuphine sebacate, is manufactured at Formosa Laboratories, Inc, Taoyuan, Taiwan. The drug product, Naldebain Extended Release Injection 75 mg/ml, is manufactured at Hsinchu Plant of UBI Pharma Inc., Hsinchu County, Taiwan.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled either during manufacturing or in the drug substance specification.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented and considered satisfactory.

The stability data presented by Formosa Laboratories, Inc are adequate to support the approved storage condition and re-test period. The packaging is double polyethylene bags purged with nitrogen and closed with cable ties. The bags are then placed into an aluminium foil bag with a silica gel desiccant. The drug substance is approved for storage at 2 – 8^{o}C with a re-test period of 60 months. The drug substance should be stored protected from moisture.

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented and considered satisfactory.

The stability data submitted is adequate to support the approved shelf-life of 36 months when stored at or below 25ºC. The drug product should be stored protected from light and in the carton before usage. The container closure system is a clear Type I glass vial fitted with rubber stopper and flip-off seal. Each vial contains 2 ml of drug product.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of dinalbuphine sebacate for use in acute postsurgical pain was based on one pivotal Phase III study, SDE-2-001. This was a randomised, double-blind, placebo-controlled study to assess the safety and efficacy of a single dose intramuscular (IM) injection of dinalbuphine sebacate for post-haemorrhoidectomy pain management. Patients with mixed haemorrhoids (both internal and external) representing both somatic and visceral pain were included, hence the use of haemorrhoids as a pain model was considered acceptable and representative of moderate to severe pain.

Patients in the study were randomised in a 1:1 ratio to receive treatment with a single IM injection of dinalbuphine sebacate 150 mg or placebo 24 hours before surgery. All patients were given the local anaesthetic, bupivacaine, prior to their scheduled surgical procedure. The post-operative analgesics were patient-controlled analgesia (PCA) ketorolac administered intravenously as needed for the first two days (Days 1 and 2) and oral ketorolac as needed for the following 5 to 8 days (Days 3 to 10). The PCA device could be removed before 48 hours as needed if PCA dosing with ketorolac was deemed not necessary by the investigator and patient. Patients were monitored for 7 days after dosing.

The primary efficacy variable was pain assessment (time-specific pain intensity) calculated as the area under the curve (AUC) of the visual analog scale (VAS) pain intensity scores through 48 hours after surgery.

A total of 221 subjects were randomised into the study and 209 randomised subjects who received at least one dose of study treatment were included in the modified intent-to-treat (mITT) population and were considered evaluable: 103 subjects in the dinalbuphine sebacate arm and 106 subjects in the placebo arm. Of these, 181 subjects (87 subjects in the dinalbuphine sebacate arm and 94 subjects in the placebo arm) who had no major protocol violations were included in the per-protocol (PP) population. The patient demographics and baseline disease characteristics were well-balanced between the treatment arms. The mean age of the study subjects was 43.8 ± 11.7 years (range 21.0 to 74.7 years) and mean body mass index (BMI) was 23.6 ± 3.4 kg/m^2 (range 17.6 to 39.2 kg/m^2). Approximately half (46.9%) of the subjects were males, 24.4% had newly diagnosed haemorrhoids and 75.6% had prior history of haemorrhoids at study entry.

Summary of Key Efficacy Results (mITT population)

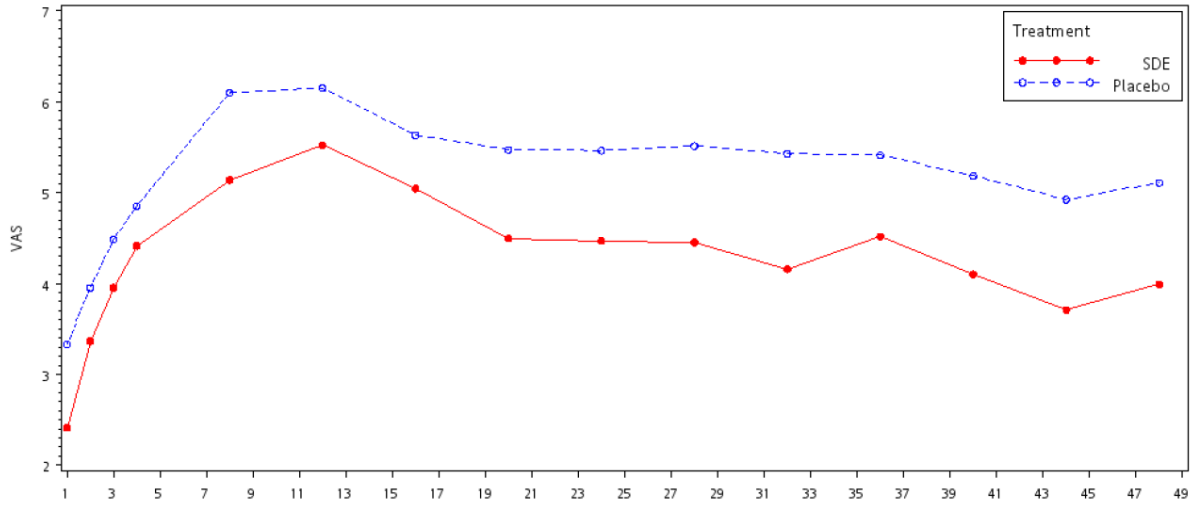
Population	Mean ± SD		Dinalbuphine sebacate – Placebo LS mean (95% CI)	p-value[a]
	Dinalbuphine sebacate (N=103)	Placebo (N=106)		
Primary endpoint				
AUC of the VAS pain intensity scores through 48 hours post-surgery				
Mean VAS scores over time				
1 hour	2.41 ± 2.59	3.33 ± 3.21	---	---
12 hours	5.53 ± 2.91	6.15 ± 2.54		
24 hours	4.47 ± 3.13	5.47 ± 3.03		
48 hours	3.99 ± 2.98	5.11 ± 3.27		
AUC_{0-24}	109.42 ± 55.04	126.71 ± 49.22	-16.86 (-31.05; -2.67)	0.0201
AUC_{0-48}	209.93 ± 111.26	253.53 ± 108.49	-42.20 (-71.68; -12.71)	0.0052
Secondary endpoints				
Consumption of ketorolac (mg) within 48 hours post-surgery				
Amount of ketorolac (mg)				
PCA	50.06 ± 45.72	82.33 ± 66.44	---	---
PCA + Oral	55.20 ± 49.51	84.21 ± 67.21		
Log-transformation of amount of ketorolac (mg)				
PCA	3.814 ± 0.852	4.199 ± 0.819	-0.381 (-0.623; -0.140)	0.0021
PCA + Oral	3.856 ± 0.890	4.228 ± 0.808	-0.366 (-0.604; -0.128)	0.0028
Consumption of oral ketorolac (mg) after 48 hours post-surgery (i.e. from Day 3 to 7)				
Amount of ketorolac (mg)				
Oral	51.36 ± 47.77	73.30 ± 55.37	---	
Log-transformation of amount of ketorolac (mg)				
Oral	3.86 ± 0.81	4.29 ± 0.69	-0.43 (-0.65, -0.21)	0.0002
VAS pain intensity scores on Days 3 to 7				
Day 3				
Morning	2.75 ± 2.30	2.79 ± 2.28	0.01 (-0.60; 0.62)	0.9755
Evening	3.51 ± 2.80	3.93 ± 2.75	-0.30 (-1.63; 1.03)	0.6538
Day 4				
Morning	3.30 ± 2.46	3.78 ± 2.73	-0.48 (-1.19; 0.24)	0.1903
Evening	3.27 ± 2.69	3.56 ± 2.67	-0.27 (-1.00, 0.46)	0.4692
Day 5				
Morning	3.05 ± 2.54	3.46 ± 2.51	-0.39 (-1.08; 0.29)	0.2603
Evening	3.20 ± 2.72	3.38 ± 2.60	-0.65 (-1.89; 0.60)	0.3056
Day 6				
Morning	2.88 ± 2.51	3.20 ± 2.66	-0.31 (-1.01; 0.39)	0.3869
Evening	2.67 ± 2.36	3.08 ± 2.63	-0.37 (-1.05; 0.31)	0.2876
Day 7				
Morning	2.50 ± 2.33	2.98 ± 2.60	-0.48 (-1.15; 0.19)	0.1593
Time from post-surgery to first use of analgesic				
Time to first use of PCA ketorolac (hours)	9.41 ± 1.00	5.54 ± 0.55	---	0.0119[b]
Time to first use of PCA + Oral analgesic (hours)	12.57 ± 1.68	4.93 ± 0.47	---	0.0093[b]
Brief pain inventory (BPI) scores				
Pain severity				
Day 1	3.52 ± 1.62	3.79 ± 1.72	-0.26 (-0.71, 0.19)	0.2507
Day 2	3.14 ± 1.50	3.57 ± 1.54	-0.41 (-0.83, -0.00)	0.0481
Day 7	3.04 ± 1.60	3.40 ± 1.73	-0.54 (-1.34, 0.25)	0.1809
Pain interference				
Day 1	3.50 ± 2.54	3.60 ± 2.24	-0.04 (-0.60, 0.52)	0.8784
Day 2	3.14 ± 2.34	3.20 ± 2.07	-0.04 (-0.50, 0.50)	0.9886
Day 7	2.94 ± 2.10	3.19 ± 2.20	-0.21 (-0.78, 0.36)	0.4690
Patient satisfaction (number (%) of subjects)				
Highly satisfied	18 (17.6%)	20 (18.9%)	---	---
Satisfied	68 (66.7%)	69 (65.1%)		

Uncertain	13 (12.7%)	10 (9.4%)		
Dissatisfied	3 (2.9%)	6 (5.7%)		
Very dissatisfied	0 (0.0%)	1 (0.9%)		

[a] Unless otherwise specified, the comparisons were performed using ANOVA with Treatment, Center effect (and Treatment x Center effect if *p*-value ≤ 0.1 in non-reduced model).
[b] The comparison was performed using log-rank test.

For the primary efficacy endpoint results, the AUC_{0-48} (mean VAS scores of pain intensity) for the dinalbuphine sebacate group showed statistically significant superiority over the placebo group in both the mITT (209.93 ± 111.26 vs 253.53 ± 108.49; p=0.0052) and PP (207.46 ± 112.41 vs 254.91 ± 106.17; p=0.0039) populations. The difference in the VAS scores between dinalbuphine sebacate and placebo was approximately 10 mm at various time-points up to 48-hours post-surgery and the difference was considered clinically meaningful.

Plot of mean VAS scores for pain intensity over time through 48 hours after haemorrhoid surgery (mITT population)



The secondary endpoints demonstrated consistent evidence in the analgesic efficacy of dinalbuphine sebacate. In the mITT population, the total amount of PCA ketorolac administered through 48 hours after surgery was lower in the dinalbuphine sebacate group compared to the placebo group (mean 50.06 vs 82.33 mg; p=0.0021). The time from post-surgery to first use of PCA ketorolac was longer in the dinalbuphine sebacate group compared to the placebo group (mean 9.41 vs 5.54 hours; p=0.0119). The total amount of oral ketorolac consumption after 48 hours post-surgery was also lower in the dinalbuphine sebacate group compared to the placebo group (mean 51.36 vs 73.30 mg).

The mean VAS scores were numerically lower in the dinalbuphine sebacate group compared to the placebo group on each assessed day (Days 3-7) in the morning and evening. The Brief Pain Inventory (BPI) scores assessed for pain severity and pain interference on Day 1, Day 2 and Day 7 decreased over time in both treatment groups. The BPI scores were numerically lower in the dinalbuphine sebacate group compared to the placebo group and there were no significant differences observed between treatment groups, except the BPI score assessed for pain severity on Day 2 (3.14 vs 3.57; p=0.0481). There was no significant difference with respect to patients' satisfaction between treatment groups. Since all subjects had access to rescue medication for pain relief, the majority of patients felt satisfied with post-surgical analgesic in both treatment groups: "highly satisfied" was rated for 17.6% of dinalbuphine

sebacate patients and 18.9% of placebo patients; “satisfied” was rated for 66.7% of dinalbuphine sebacate patients and 65.1% of placebo patients.

Overall, the study met its primary endpoint and the overall results adequately supported the efficacy of dinalbuphine sebacate for use in moderate to severe acute postsurgical pain.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of dinalbuphine sebacate was based primarily on safety data derived from the pivotal Phase III study, SDE-2-001, which included a total of 221 subjects (109 subjects in the dinalbuphine sebacate group and 112 subjects in the placebo group) with pre-diagnosed haemorrhoid exposed to a single dose of 150 mg IM dinalbuphine sebacate or placebo 24 hours prior to haemorrhoidectomy.

Overview of adverse events in study SDE-2-001

Events	Dinalbuphine sebacate (N=109)	Placebo (N=112)
Treatment-emergent adverse events (AEs)	76 (69.7%)	62 (55.4%)
Treatment-related AEs	31 (28.4%)	13 (11.6%)
Serious AEs (SAEs)	8 (7.3%)	2 (1.8%)
Treatment-related SAEs	2 (1.8%)	0
Discontinuations due to AEs	0	0
Deaths	0	0

A total of 76 subjects (69.7%) in the dinalbuphine sebacate group and 62 subjects (55.4%) in the placebo group reported at least one AE. The most frequently reported AEs and their incidences (dinalbuphine sebacate vs placebo) were pyrexia (37.6% vs 17.9%), dizziness (16.5% vs 3.6%), constipation (11.9% vs 10.7%) and dysuria (11.0% vs 9.8%). The majority of AEs were reported as mild in severity. Of three AEs reported as severe, one AE (dizziness) was considered as probably related to the study treatment.

Treatment-related AEs were reported by 31 subjects (28.4%) in the dinalbuphine sebacate group and 13 subjects (11.6%) in the placebo group, and included pyrexia (16.5% vs 8.9%), dizziness (6.4% vs 0.9%), vomiting (2.8% vs 0%), and nausea (1.8% vs 0%).

Injection site reactions were reported at a higher incidence in the dinalbuphine sebacate group compared to the placebo group. There were 30 subjects (27.5%) in the dinalbuphine sebacate group and 7 subjects (6.3%) in the placebo group who experienced erythema or swelling at the injection site during the study. The mean recovery time was greater in the dinalbuphine sebacate group than in the placebo group (16.6 vs 2.7 hours), but majority of subjects recovered without erythema or swelling present at final visit.

Serious AEs (SAEs) were reported for 8 subjects (7.3%) in the dinalbuphine sebacate group and 2 subjects (1.8%) in the placebo group. The most commonly reported SAE was pyrexia (4.6% vs 0%), two of which were considered possibly treatment-related. The remaining SAEs were reported in one subject each, none of which were considered treatment-related. There were no discontinuations due to AEs in the dinalbuphine sebacate group. No deaths were reported in the study.

Based on the known pharmacology of nalbuphine as a mixed opioid antagonist-agonist, the risks of addiction, abuse and misuse are expected be lower than that of other opioids (e.g.

morphine), although the risks cannot be entirely excluded and appropriate warnings and precautions have been included in the package insert regarding the potential for these risks.

Overall, the safety profile of dinalbuphine sebacate demonstrated in the clinical study was consistent with what is expected for nalbuphine, and the main safety risks (injection site reactions, pyrexia, dizziness, constipation, vomiting, nausea) were acceptable and manageable. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Post-operative pain relief is currently managed by multimodal analgesia comprising a variety of analgesic medications (e.g. non-steroidal anti-inflammatory drugs [NSAIDs] and opioids) and techniques that target different mechanisms of action. For moderate to severe pain post-surgery, opioid analgesics (such as morphine, tramadol, oxycodone, fentanyl) are commonly used. However, these opioids come with inherent risks such as severe respiratory depression, drug tolerance, physical dependence and abuse-related issues.

Dinalbuphine sebacate is a prodrug of nalbuphine, which is a mixed opioid antagonist-agonist, and has a ceiling effect in terms of respiratory depression and potentially a lower risk for addiction and abuse compared to full opioid agonists. The single-dose regimen that is to be administered prior to surgery and the extended duration of action lasting several days provides an advantage over the need for continuous administration of a short-acting opioid post-surgery.

The benefits of Naldebain Extended-Release Injection for use in post-surgical pain had been demonstrated in terms of reduction in pain intensity as measured by the AUC of the VAS pain intensity scores through 48 hours after haemorrhoidectomy surgery. The AUC_{0-48} (mean VAS scores of pain intensity) for the dinalbuphine sebacate group showed statistically significant superiority compared to the placebo group in both the mITT (209.93 ± 111.26 vs 253.53 ± 108.49; p=0.0052) and PP (207.46 ± 112.41 vs 254.91 ± 106.17; p=0.0039) populations.

The key secondary endpoints provided further support for the efficacy of dinalbuphine sebacate in terms of a lower consumption of PCA ketorolac (mean 50.06 vs 82.33 mg; p=0.0021), prolonged time to first use of PCA ketorolac (mean 9.41 vs 5.54 hours; p=0.0119), and lower total amount of oral ketorolac consumption (mean 51.36 vs 73.30 mg) in the dinalbuphine sebacate group compared to placebo.

The safety profile of dinalbuphine sebacate was consistent with what is expected for nalbuphine, and the main safety risks were acceptable and manageable. Injection site reactions, in particular erythema or swelling at the injection site, were the main safety risks (27.5% with dinalbuphine sebacate vs 6.3% with placebo). The other treatment-related AEs noted were pyrexia (16.5% vs 8.9%), dizziness (6.4% vs 0.9%), vomiting (2.8% vs 0%), and nausea (1.8% vs 0%), which are known AEs of opioids.

Overall, taking into consideration the benefits demonstrated in terms of a clinically meaningful pain relief and the acceptable and manageable safety profile, the benefit-risk profile of Naldebain Extended-Release Injection to be administered as a single-dose prior to surgery for the relief of moderate to severe acute postsurgical pain was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Naldebain for the relief of moderate to severe acute postsurgical pain was deemed favourable and approval of the product registration was granted on 15 December 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

NALDEBAIN (dinalbuphine sebacate) Extended Release Injection 75mg/mL

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NALDEBAIN is indicated for the relief of moderate to severe acute postsurgical pain. *[see Clinical studies (13)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Administer intramuscularly at a dose of 150 mg single dose.
It is not necessary to adjust dosage based on body surface area or body weight.
NALDEBAIN is an extended release formulation, it should be taken into consideration that it takes 12~24 hours to achieve therapeutic concentration.
NALDEBAIN is not adequate for administration in patients with urgent analgesics need.
NALDEBAIN is fixed dose package and only for single dose use. Safety and effectiveness for repeat-dose use have not been established
Except for nalbuphine and ketorolac, studies of concomitant use with other drugs including general anesthetic have not been conducted.

2.2 Instructions for Use

NALDEBAIN should be administered only via the intramuscular route.

Instructions for administration:

1. Clean the vial top with an alcohol swab before use.
2. Draw up 2 mL of drug into syringe.
3. After preparing the skin, inject in the upper outer quadrant of the gluteus maximus. The solution is viscous and oily. Slow injection is recommended.
4. Slightly applying pressure to the injection site to prevent drug solution leakage.
5. Do not massage the injection site.

3 DOSAGE FORMS AND STRENGTHS

NALDEBAIN® ER Injection, 2 mL/vial is a sterile, clear and light yellow oily solution containing 75 mg/mL dinalbuphine sebacate. The product is supplied in a glass vial.

4 CONTRAINDICATION

NALDEBAIN is for administration via the intramuscular route. It is prohibited for intravenous administration.
NALDEBAIN is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Hypersensitivity to nalbuphine, sesame oil or benzyl benzoate in NALDEBAIN.

5 WARNINGS AND PRECAUTION

5.1 Use in Ambulatory Patients

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

5.2 Use in Emergency Procedures

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

5.3 Use in Pregnancy (Other Than Labor)

Severe fetal bradycardia has been reported when nalbuphine is administered during labor. Although there are no reports of developmental toxicity, including teratogenicity, or harm to the fetus in reproduction studies, this drug should be used in pregnancy only if clearly needed, if the potential benefit outweighs the risk to the fetus.

5.4 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. Some of these events have been life-threatening. 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. Nalbuphine hydrochloride or NALDEBAIN should be used during labor and delivery only if clearly indicated and only if the potential benefit outweighs the risk to the infant. Newborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if Nalbuphine hydrochloride or NALDEBAIN has been used.

5.5 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 CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, nalbuphine /NALDEBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution.

5.6 Renal Impairment

Because nalbuphine is excreted by the kidneys, NALDEBAIN should be used with caution in patients with renal impairment.

5.7 Hepatic Impairment

NALDEBAIN should be used with caution in patients with liver dysfunction. Because nalbuphine is metabolized in the liver and excreted by the kidneys, NALDEBAIN should be used with caution in patients with liver dysfunction.

5.8 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of NALDEBAIN, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with NALDEBAIN.

Overestimating the opioids dosage when converting patients from another opioid product can result in a fatal overdose with the first dose. Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

5.9 Neonatal Opioid Withdrawal Syndrome

Prolonged use of opioids during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

5.10 Risk of Concomitant Use or Discontinuation with Cytochrome P450 3A4 Inhibitors and Inducers

Risk of Increased nalbuphine Plasma Concentrations

Increased plasma concentrations of nalbuphine, which may result in prolonged opioid adverse reactions and exacerbated respiratory depression, may occur when NALDEBAIN is used under the following conditions:

- In patients taking a moderate or strong CYP3A4 Inhibitor
- Discontinuation of a CYP3A4 inducer

Closely monitor these patients for respiratory depression and sedation at frequent intervals.

Risk of Lower than Expected nalbuphine Plasma Concentrations

Lower than expected concentrations of nalbuphine, which may lead to decreased efficacy, may occur under the following conditions:

- Concomitant use of NALDEBAIN with CYP3A4 inducers
- Discontinuation of a moderate or strong CYP3A4 inhibitor

Closely monitor these patients at frequent intervals and consider supplemental doses of other analgesics.

5.11 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of NALDEBAIN with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol).

Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see PRECAUTIONS; Drug Interactions].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when NALDEBAIN is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see PRECAUTIONS; Drug Interactions and Information for Patients].

5.12 Risk of Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of NALDEBAIN in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: NALDEBAIN-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of use of NALDEBAIN.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating NALDEBAIN and when NALDEBAIN is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

5.13 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than 1 month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.14 Severe Hypotension

Nalbuphine may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating the dosage of NALDEBAIN. In patients with circulatory shock, NALDEBAIN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of NALDEBAIN in patients with circulatory shock.

5.15 Risks of Use in Patients with Gastrointestinal Conditions

Nalbuphine is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The nalbuphine in NALDEBAIN may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.16 Increased Risk of Seizures in Patients with Seizure Disorders

The nalbuphine in NALDEBAIN may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during NALDEBAIN therapy.

5.17 Addiction, Abuse, and Misuse

Nalbuphine hydrochloride is a synthetic opioid agonist-antagonist analgesic. As an opioid, NALDEBAIN exposes users to the risks of addiction, abuse, and misuse.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed NALDEBAIN. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing NALDEBAIN. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.18 Withdrawal

The use of NALDEBAIN, a mixed agonist/antagonist opioid analgesic, in patients who are receiving a full opioid agonist analgesic may reduce the analgesic effect and/or precipitate withdrawal symptoms. Avoid concomitant use of NALDEBAIN with a full opioid agonist analgesic in a physically dependent patient.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials

A total of 109 subjects received single dose of 150mg NALDEBAIN were included in the population for safety evaluation of NALDEBAIN.

6.1.1 Overall evaluation of the safety profile in clinical studies, the most clinically significant adverse reactions observed with NALDEBAIN 150mg were nausea, vomiting, injection site reaction, pyrexia and dizziness. All those reactions are assessed as mild to moderate in severity. The incidence of adverse reactions listed in Table 1.

Table 1 Summary of ADR Incidence

Adverse drug reaction	NALDEBAIN N=109		Placebo N=112	
	n	%	n	%
Injection site reaction	30	27.5%	7	6.3%
Pyrexia	18	16.5%	10	8.9%
Dizziness	7	6.4%	1	0.9%
Vomiting	3	2.8%	0	0.0%
Nausea	2	1.8%	0	0.0%
Somnolence	1	0.9%	0	0.0%

Most of the subjects in phase III studies with injection site reaction were recovered present at final visit (Day 7~10). In a bioavailability study, the study period after NALDEBAIN administration is 14 days. The injection site reaction is monitored until end of the study. Part of subjects recovered on Day 8, and all subjects recovered on Day 12. All the subjects felt the symptoms is tolerable and finished the study. The observation is all the injection site reaction recovered at the end of the study. That means the reaction is tolerable and reversible

6.1.2 Overall evaluation of the safety profile in clinical studies, the frequency of adverse events whether drug related or not in NALDEBAIN and placebo treatment groups is summarized in Table 2.

Table 2 Incidence of subjects with TEAE by body system-Safety population

System Organ Class **Preferred Term**	**NALDEBAIN (N = 109)**	**Placebo (N = 112)**	**Overall (N = 221)**
General disorders and administration site conditions			
Chills	1 (0.9%)	1 (0.9%)	2 (0.9%)
Fatigue	1 (0.9%)	3 (2.7%)	4 (1.8%)
Feeling cold	2 (1.8%)	0 (0.0%)	2 (0.9%)
Injection site swelling	0 (0.0%)	1 (0.9%)	1 (0.5%)
Pyrexia	41 (37.6%)	20 (17.9%)	61 (27.6%)
Gastrointestinal disorders			
Abdominal discomfort	0 (0.0%)	1 (0.9%)	1 (0.5%)
Abdominal distension	4 (3.7%)	3 (2.7%)	7 (3.2%)
Abdominal pain	1 (0.9%)	0 (0.0%)	1 (0.5%)
Abdominal pain lower	1 (0.9%)	0 (0.0%)	1 (0.5%)
Abdominal pain upper	2 (1.8%)	2 (1.8%)	4 (1.8%)
Anal pruritus	0 (0.0%)	1 (0.9%)	1 (0.5%)
Constipation	13 (11.9%)	12 (10.7%)	25 (11.3%)
Diarrhoea	0 (0.0%)	1 (0.9%)	1 (0.5%)
Faecaloma	1 (0.9%)	0 (0.0%)	1 (0.5%)
Flatulence	1 (0.9%)	0 (0.0%)	1 (0.5%)
Gastrointestinal motility disorder	0 (0.0%)	1 (0.9%)	1 (0.5%)
Intestinal obstruction	1 (0.9%)	0 (0.0%)	1 (0.5%)
Irritable bowel syndrome	1 (0.9%)	7 (6.3%)	8 (3.6%)
Nausea	5 (4.6%)	3 (2.7%)	8 (3.6%)
Oesophageal ulcer	1 (0.9%)	0 (0.0%)	1 (0.5%)
Vomiting	10 (9.2%)	1 (0.9%)	11 (5.0%)
Renal and urinary disorders			
Cystitis noninfective	1 (0.9%)	0 (0.0%)	1 (0.5%)
Dysuria	12 (11.0%)	11 (9.8%)	23 (10.4%)
Urinary retention	6 (5.5%)	6 (5.4%)	12 (5.4%)
Nervous system disorders			
Dizziness	18 (16.5%)	4 (3.6%)	22 (10.0%)

System Organ Class Preferred Term	NALDEBAIN (N = 109)	Placebo (N = 112)	Overall (N = 221)
Headache	4 (3.7%)	4 (3.6%)	8 (3.6%)
Hypoaesthesia	1 (0.9%)	0 (0.0%)	1 (0.5%)
Poor quality sleep	0 (0.0%)	2 (1.8%)	2 (0.9%)
Somnolence	1 (0.9%)	0 (0.0%)	1 (0.5%)
Psychiatric disorders			
Anxiety	1 (0.9%)	5 (4.5%)	6 (2.7%)
Insomnia	1 (0.9%)	5 (4.5%)	6 (2.7%)
Nervousness	1 (0.9%)	0 (0.0%)	1 (0.5%)
Injury, poisoning and procedural complications			
Post procedural haemorrhage	1 (0.9%)	2 (1.8%)	3 (1.4%)
Post procedural swelling	3 (2.8%)	1 (0.9%)	4 (1.8%)
Infections and infestations			
Injection site cellulitis	1 (0.9%)	0 (0.0%)	1 (0.5%)
Nasopharyngitis	0 (0.0%)	1 (0.9%)	1 (0.5%)
Urinary tract infection	1 (0.9%)	2 (1.8%)	3 (1.4%)
Investigations			
Blood pressure decreased	2 (1.8%)	0 (0%)	2 (0.9%)
Blood pressure systolic decreased	1 (0.9%)	0 (0%)	1 (0.5%)
Liver function test abnormal	2 (1.8%)	0 (0%)	2 (0.9%)
Respiratory, thoracic and mediastinal disorders			
Cough	2 (1.8%)	2 (1.8%)	4 (1.8%)
Rhinorrhoea	0 (0.0%)	1 (0.9%)	1 (0.5%)
Skin and subcutaneous tissue disorders			
Eczema	0 (0%)	1 (0.9%)	1 (0.5%)
Hyperhidrosis	1 (0.9%)	0 (0%)	1 (0.5%)
Rash pruritic	0 (0%)	1 (0.9%)	1 (0.5%)
Urticaria	1 (0.9%)	0 (0%)	1 (0.5%)
Ear and labyrinth disorders			
Vertigo	2 (1.8%)	0 (0%)	2 (0.9%)
Eye disorders			
Conjunctival pallor	0 (0%)	1 (0.9%)	1 (0.5%)
Scleral haemorrhage	0 (0%)	1 (0.9%)	1 (0.5%)
Blood and lymphatic system disorders			
Anaemia	0 (0%)	1 (0.9%)	1 (0.5%)
Cardiac disorders			
Palpitations	1 (0.9%)	0 (0%)	1 (0.5%)
Metabolism and nutrition disorders			
Decreased appetite	0 (0%)	1 (0.9%)	1 (0.5%)
Musculoskeletal and connective tissue discorders			
Myalgia	0 (0%)	1 (0.9%)	1 (0.5%)
Vascular disorders			
Hypertension	0 (0%)	1 (0.9%)	1 (0.5%)

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

Studies of NALDEBAIN concomitant use with general anesthetic have not been conducted.

Although nalbuphine 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 nalbuphine. Therefore, patients receiving an opioid analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NALDEBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.
In phase III studies, all subjects were given local anesthetic (bupivacaine) prior to surgery (99%). 94% of subjects combined using local anesthetics Lidocaine. About 2 % subjects used midazolam. Reviewing overall adverse events, administration of local general anesthetics, bupivacaine, lidocaine, propofol and midazolam in combination with NALDEBAIN in phase III studies does not result in clinical significant adverse reactions.

7.2 Opioids

Studies of NALDEBAIN concomitant use with opiates have not been conducted. Since NALDEBAIN is nalbuphine's prodrug, the concomitant use with opioids could refer to experiences of nalbuphine hydrochloride.
When NALDEBAIN combine used with nalbuphine, the dose of nalbuphine should not exceed 80 mg per day or 20 mg Q6H.

7.3 General anesthetic

Studies of NALDEBAIN concomitant use with general anesthetic, including inhaled anesthetic, intravenous administered anesthetic like opioid and benzodiazepine, have not been conducted. Since NALDEBAIN is nalbuphine's prodrug, the concomitant use with general anesthetics could refer to experiences of nalbuphine hydrochloride. According to references, there is no clinically significant safety concern without dosage adjustment of anesthetic.

7.4 CYP3A4 inhibitors/inducers

Initiation of CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of Naldebain.

7.5 Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome.

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue NALDEBAIN if serotonin syndrome is suspected.

7.6 Muscle Relaxants

Nalbuphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of the muscle relaxant as necessary.

7.7 Diuretics

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

7.8 Anticholinergic Drugs

The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Monitor patients for signs of urinary retention or reduced gastric motility when NALDEBAIN is used concomitantly with anticholinergic drugs.

7.9 Monoamine Oxidase Inhibitors (MAOIs)

MAOI (e.g., phenelzine, tranylcypromine, linezolid) interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma). The use of NALDEBAIN is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

If urgent use of an opioid is necessary, closely monitor blood pressure and signs and symptoms of CNS and respiratory depression.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B
Reproduction studies have been performed in rats by subcutaneous administration of nalbuphine up to 100 mg/kg/day, or 590 mg/m2/day which is approximately 6 times the MRHD(Maximum Recommended Human Dose), and in rabbits by intravenous administration of nalbuphine up to 32 mg/kg/day, or 378 mg/m2/day which is approximately 4 times the MRHD. The results did not reveal evidence of developmental toxicity, including teratogenicity, or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NALDEBAIN should be used during pregnancy only if clearly needed.

Non-teratogenic Effects:
Neonatal body weight and survival rates were reduced at birth and during lactation when nalbuphine was subcutaneously administered to female and male 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 4 times the maximum recommended human dose.

8.2 Labor and Delivery

See 5.4.

8.3 Nursing Mothers

Limited data suggest that nalbuphine (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 NALDEBAIN is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Not necessary to adjust dose in geriatric population.

9 OVERDOSAGE

There is no incidence of NALDEBAIN administering overdose in clinical trial.

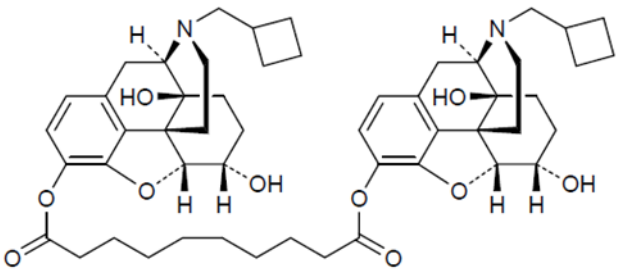
The suggestion for overdosage is immediate intravenous administration an opiate antagonist such as naloxone or nalmefene is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

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

10 DESCRIPTION

NALDEBAIN Extended Release Injection, a prodrug of nalbuphine, contains dinalbuphine sebacate as the active ingredient.

Dinalbuphine sebacate is a synthetic nalbuphine prodrug contains two nalbuphine molecules joined by sebacoyl ester. The chemical name for dinalbuphine sebacate is: bis[17-(cyclobutylmethyl)-4,5α-epoxy6α,14-dihydroxymorphinan-3-yl] decanedioate. Dinalbuphine sebacate molecular weight is 881.10 and is insoluble in water. Dinalbuphine sebacate is soluble in dichloromethane and slightly soluble in methanol. The molecular formula is $C_{52}H_{68}N_2O_{10}$. The structural formula is



NALDEBAIN Extended Release Injection is a sterile, clear and light yellow oily solution. The product is packed in a 2-mL vial used for muscular injection. The product is supplied in a 2-mL glass vial.

Inactive ingredients include: benzyl benzoate, and sesame oil (contains BHT at 750 – 1000ppm as antioxidant.).

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Dinalbuphine sebacate is a synthetic nalbuphine prodrug. The dosage form is a sterile oil solution, which is suitable for intramuscular injection. Dinalbuphine sebacate contains two nalbuphine molecules joined by sebacoyl ester which is rapidly hydrolyzed to nalbuphine by esterase. Nalbuphine is the active moiety. Nalbuphine is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis. Receptor studies show that nalbuphine binds to mu, kappa, and delta receptors, but not to sigma receptors. Nalbuphine is primarily a kappa agonist/partial mu antagonist analgesic.

11.2 Pharmacodynamics

The pharmacodynamics of dinalbuphine sebacate is from nalbuphine.
Nalbuphine may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, nalbuphine exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression in the absence of other CNS active medications affecting respiration. Nalbuphine 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), nalbuphine may partially reverse or block opioid-induced respiratory depression from the mu agonist analgesic. Nalbuphine may precipitate withdrawal in patients dependent on opioid drugs. NALDEBAIN should be used with caution in patients who have been receiving mu opioid analgesics on a regular basis.

11.3 Pharmacokinetics

Absorption

Following intramuscular administration 150mg of dinalbuphine sebacate, the drug is absorbed and rapidly hydrolyzed as nalbuphine with peak concentrations (Cmax) achieved at 64.0±9.3 hours. The mean Cmax is estimated to be 15.4±6.4 ng/mL.

Metabolism

Dinalbuphine sebacate is metabolized primarily by esterase. Biotransformation studies showed that over 90% of the prodrug was converted to nalbuphine in about 30 min in fresh human whole blood.
Nalbuphine is metabolized by Cytochrome P450s and phase II enzyme UGTs (uridinyl diphosphate glucuronosyltransferases), and produce glucuronide metabolites.

Distribution

The mean apparent volume of distribution in healthy volunteers after administration 150 mg NALDEBAIN is estimated to be 10628 ± 4403 L
In vitro plasma protein binding study suggest that dinalbuphine sebacate protein binding is about 90% in human plasma.
Dinalbuphine sebacate and nalbuphine did partition into red blood cells but not to a greater extent than to plasma. The RBC partition coefficients, $K_{RBC/PL}$, for dinalbuphine sebacate determined to be 1.20； nalbuphine determined to be 1.24.

Excretion
Nalbuphine is mainly excreted by the kidneys. Following intramuscular administration 150mg of dinalbuphine sebacate, the drug is absorbed and rapidly hydrolyzed as nalbuphine. The elimination half-life of nalbuphine was 83.2 ± 46.4 hr. Mean clearance of nalbuphine is 100 ± 11 L/h.
Less than 4% nalbuphine of each dose was recovered in urine.
Drug Interaction
No drug interaction studies have been conducted [see Drug Interactions (7)].

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
No carcinogenesis study was conducted with dinalbuphine sebacate. According to reference, long term carcinogenicity studies were performed in rats (24 months) and mice (19 months) by oral administration at doses up to 200 mg/kg (1180 mg/m^2) and 200 mg/kg (600 mg/m^2) per day, respectively. There was no evidence of an increase in tumors in either species related to nalbuphine administration.

Mutagenesis
Dinalbuphine sebacate did not show genotoxic activity in the in vivo mouse peripheral blood micronucleus assay.
According to reference, nalbuphine did not have mutagenic activity in the AMES test with four bacterial strains, in the Chinese Hamster Ovary HGPRT assays or in the Sister Chromatids Exchange Assay. However, nalbuphine induced an increased frequency of mutation in the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test of the cytogenicity bone marrow assay in rats.

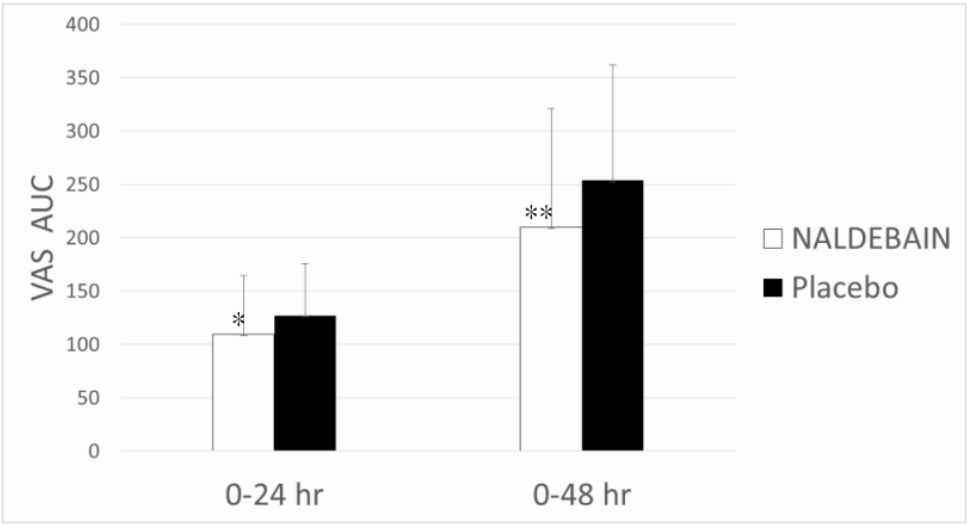
Impairment of Fertility
No reproduction toxicity study was conducted with dinalbuphine sebacate. In reproductive and developmental toxicity studies in rats, nalbuphine did not affect fertility at subcutaneous doses up to 56 mg/kg/day or 330 mg/m^2/day.

13 CLINICAL STUDIES

A multicenter, randomized, double-blind, placebo-controlled phase III study evaluated the safety and efficacy of 150 mg NALDEBAIN in patients undergoing hemorrhoidectomy. There are 103 subjects in NALDEBAIN group while 106 subjects in placebo group. 24±12hrs prior to hemorrhoidectomies, the subjects were treated with single IM injection of NALDEBAIN 150mg. The post-operative analgesics were PCA dosing with ketorolac as needed for the first two days (Day 1 and 2) and oral dosing with ketorolac as needed for the following 5-8 days (Day 3 to 10). The primary objective of this study is pain assessment (time-specific pain intensity) calculated as the area under the curve (AUC) of VAS pain intensity scores through 48 hours after surgery (AUC_{0-48}). There was a significant treatment effect for NALDEBAIN compared to placebo through 48 hours after surgery (p=0.0052) (Figure 1).

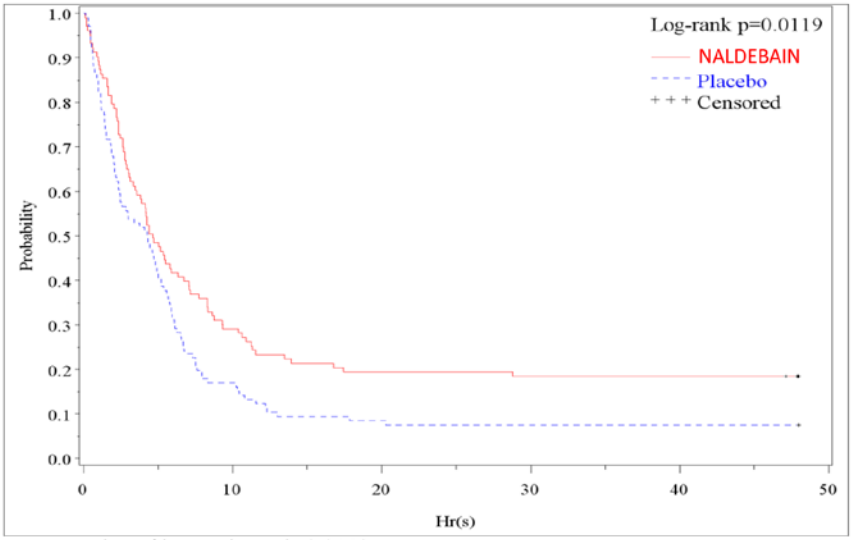
In this clinical study, NALDEBAIN demonstrated a significant reduction in pain intensity compared to placebo for up to 48 hours after surgery, equals to 72 hours after administration. The difference in mean pain intensity between treatment groups occurred during the 24 and 48 hours after surgery, which means following 48 and 72 hours study drug administration. Subjects treated with NALDEBAIN took significantly longer periods of time for the first use of Ketorolac via PCA than those in placebo group, 9.41 hours in NALDEBAIN group, 5.54 hours in placebo group. Figure 2 shows the probability of subjects who does not use the PCA within 48 hours after surgery. The total amount of Ketorolac administered by PCA through 48 hours after surgery in NALDEBAIN group is 50.06 mg while in placebo group is 82.33 mg. From Day 3 to Day 7 after surgery, there was a significant decrease in oral analgesics consumption, 51.36 mg in NALDEBAIN group, 73.30 mg in placebo group. The total amount of Ketorolac administered by PCA through 48 hours after surgery was compared between treatment groups by using an ANOVA model on log-transformed data. The results of statistical analysis are summarized in Table 3. The total amount of PCA Ketorolac consumption in NALDEBAIN group is less than placebo group in both mITT and PP populations with a statistical significance level of 5% (p=0.0021 in mITT population and p=0.0075 in PP population). All enrolled subjects have administered the oral Ketorolac after 48 hours post-operation. Both the mean and median for consumption of oral Ketorolac after 48 hours post-hemorrhoidectomy were lower in NALDEBAIN group than those in placebo group and the differences between treatment groups were observed in both mITT and PP populations. Based on the results of statistical analyzed by using an ANOVA model on log-transformed data (Table 4), the total amount of oral Ketorolac consumption in NALDEBAIN group was less in both mITT and PP populations comparing to that in placebo group with a statistical significance level of 5%.

Figure 1. Cumulative pain score (VAS AUC) through 24 hours and 48 hours after hemorrhoid operation-mITT



*p<0.05. ** p<0.01 AUC: area under the curve.

Figure 2. Kaplan-Meier graph of time from post-operation to the first use of PCA Ketorolac (the probability of the events not happening within a time period)-mITT



Note: *p*-value of log-rank test is 0.0119

Censored: observation until 48 hrs after surgery

Table 3. Statistical analysis of Ketorolac consumption (mg) within 48 hours after surgery by treatment-mITT/PP

Population	Mean ± SD (Nobs[5])		NALDEBAIN - Placebo	*p*-value[2]
	NALDEBAIN	Placebo	LS-mean [95% CI][1]	
mITT				
N	103	106		
PCA[3]	3.814 ± 0.852 (84)	4.199 ± 0.819 (99)	-0.381 [-0.623;-0.140]	0.0021*
PCA+Oral[4]	3.856 ± 0.890 (87)	4.228 ± 0.808 (99)	-0.366 [-0.604;-0.128]	0.0028*
PP (N)				
N	87	94		
PCA[3]	3.854 ± 0.838 (70)	4.197 ± 0.803 (87)	-0.350 [-0.605;-0.095]	0.0075*
PCA+Oral[4]	3.898 ± 0.865 (72)	4.230 ± 0.789 (87)	-0.336 [-0.585;-0.087]	0.0086*

Note: Log-transformation of amount of ketorolac by PCA was used.

[1]95% CI (Confidence Interval): [lower bound; upper bound]

[2]ANOVA with Treatment, Center effect (and Treatment×Center effect if *p*-value ≤ 0.1 in non-reduced model)

[3]The Ketorolac administered by PCA plus the administration of rescue medication, adjusted to the amount of PCA Ketorolac

[4]All sorts of analgesic administered (including Bain®, PCA and Oral Ketorolac)

[5]NObs = Number of Observation

*Significant at 5% level

Table 4. Statistical analysis for consumption of oral Ketorolac after 48 hours post-surgery by treatment-mITT/PP

Population	Mean ± SD (Nobs[1])		NALDEBAIN - Placebo	*p*-value[3]
	NALDEBAIN	Placebo	LS-mean [95% CI][2]	
mITT (N)	103	106		
Oral[4]	3.86±0.81 (84)	4.29±0.69 (88)	-0.43 [-0.65;-0.21]	0.0002*
PP (N)	87	94		
Oral[4]	3.87±0.83 (70)	4.32±0.67 (78)	-0.45 [-0.69;-0.21]	0.0003*

Note: Log-transformation of amount of oral ketorolac was used

[1]NObs = Number of Observation

[2]95% CI (Confidence Interval): [lower bound; upper bound]

[3]ANOVA with Treatment, Center effect (and Treatment×Center effect if *p*-value ≤ 0.1 in non-reduced model)

[4]The consumption of oral Ketorolac after 48 hours post-surgery to the end of study

*Significant at 5% level

14 HOW SUPPLIED/STORAGE AND HANDLING

NALDEBAIN should be stored at temperature below 25℃ and avoid direct light exposure. Please store in the carton before usage.
NALDEBAIN ER INJECTION (dinalbuphine sebacate injection) is available in single-use vials. 2 mL single use vial (75 mg/mL) for IM injection is packaged in a carton.

Product owner: Lumosa Therapeutics Co., Ltd.

4F, No. 3-2, Park Street, Nangang District, Taipei, 11503, Taiwan

Manufacturer: Hsinchu Plant of UBI Pharma Inc.

No.45, Guangfu N. Rd., Hukou Township, Hsinchu County 30351, Taiwan, R.O.C.