Drug Enforcement Administration
Diversion Control Division
Drug & Chemical Evaluation Section

NALBUPHINE HYDROCHLORIDE

(Trade Name: Nubain®)

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Introduction:

In the search for narcotic analgesics with less abuse potential, a number of synthetic opiates were developed. These substances are referred to as mixed agonist-antagonists analgesics. This group of substances include Nalbuphine (Nubain), which was approved for marketing in the United States in 1979. Of those marketed in the United States, Nalbuphine remains the only narcotic analgesic of this type not controlled under the Controlled Substances Act (CSA).

Licit Uses:

Nalbuphine is approved for use in the United States as the hydrochloride salt in an injectable formulation (10 or 20 mg/mL). It is available by brand name (Nubain) and generic formulations. Nalbuphine is indicated for the treatment of moderate to severe acute pain. According to the IQVIA National Prescription Audit™, total prescriptions dispensed for nalbuphine in the United States were 12,315 in 2018; 951 in 2020; 3,343 in 2022; and 2,711 in 2024.

Chemistry:

Nalbuphine hydrochloride (Nubain) is classified as a synthetic opioid agonist-antagonist. Chemically, it is related to the opioid antagonist, naloxone, and the potent opioid agonist, oxymorphone. The chemical name for nalbuphine is 17-(cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-triol hydrochloride. It is soluble in water and ethanol and is available only as an injectable solution.

Pharmacology:

Nalbuphine is a potent analgesic. Its analgesic potency is essentially equivalent to morphine. It binds to mu, kappa, and delta opioid receptors. Nalbuphine is metabolized by the liver and excreted by the kidneys.

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

Nalbuphine, like other potent opioids, is associated with respiratory depression. Unlike morphine and other potent mu agonists, nalbuphine produces less respiratory depression as the dose is increased due to its agonist- antagonist “ceiling” effect. Nalbuphine produces considerable sedation and may impair mental and physical abilities in the performance of tasks like driving automobiles or operating machinery.

Nalbuphine may cause psychological or physical dependence and tolerance. Abrupt discontinuation after prolonged use can cause signs and symptoms of opioid withdrawal.

Illicit Uses:

As an injectable formulation, nalbuphine is primarily used in hospitals and rarely prescribed by physicians compared to other opioid analgesics. In addition, as a drug of abuse, nalbuphine is less attractive as a substitute to heroin addicts or highly tolerant opioid abusers due to its potent antagonist effects. Nalbuphine is 10 times more potent than pentazocine as an antagonist and will precipitate withdrawal in an opiate-tolerant individual. A limited number of anecdotal reports suggests that nalbuphine is abused by health care professionals and body builders (anabolic steroid users).

User Population:

The American Association of Poison Control Centers’ 2022 Annual Report indicates that there was one single substance exposure related to nalbuphine in that year. For 2021, there were a total of four exposures, of which one was single substance exposure. No deaths were associated with nalbuphine in 2021 or 2022.

Illicit Distribution:

Nalbuphine is rarely encountered by law enforcement personnel or submitted to forensic laboratories for analysis. This may be, in part, due to its non-controlled status.

The Drug Enforcement Administration’s National Forensic Laboratory Information System (NFLIS) Drug database collects scientifically verified data on drug items and cases submitted to and analyzed by participating federal, state, and local forensic drug laboratories. NFLIS-Drug received 2 reports of nalbuphine in 2015 and no more than 1 each year since.

Control Status:

Nalbuphine is not a controlled substance under the CSA.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 571-362-4250, Telephone 571-362-3249, or Email DPE@dea.gov.