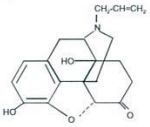
NALOXONE INJECTION "G.B.L." 0.4mg/ml
(naloxone hydrochloride injection, USP)

Rx Only

Licence Number: G-9234 048184 Opioid Antagonist

DESCRIPTION

Naloxone Injection "G.B.L." (naloxone hydrochloride injection, USP), an opioid antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



• HCl

Naloxone hydrochloride appears as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Naloxone Injection "G.B.L." is a sterile solution, and has 3 routes as intravenous, intramuscular and subcutaneous administration in concentration of 0.02mg, 0.4 mg and 1.0 mg of naloxone hydrochloride per mL. The 0.02mg/mL and the 0.4 mg/mL vial contain 8.6 mg/mL of sodium chloride respectively. The 1.0mg/mL vial contains 8.35 mg/mL of sodium chloride. The 0.4 mg/mL vial and 1.0 mg/mL vial also contain 2.0 mg/mL of methylparaben and propylparaben as preservatives in a ratio of 9:1. pH is adjusted to be 3.5±0.5 with hydrochloric acid.

Naloxone Injection "G.B.L." has 3 concentrations free of paraben: 0.02mg, 0.4 mg and 1.0 mg of naloxone hydrochlorider per mL. Each concentration contains 9.0 mg of sodium chloride per mL. PH is adjusted to be 3.5±0.5 with hydrochloric acid.

[According to Public Available Reference]

CLINICAL PHARMACOLOGY

Complete or Partial Reversal of Opioid Depression

Naloxone Injection "G.B.L." prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

Naloxone Injection "G.B.L." is an essentially pure opioid antagonist, meaning, it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. Naloxone Injection "G.B.L." does not produce respiratory depression, psychotomimetic effects or pupillary constriction. Therefore, Naloxone Injection "G.B.L." exhibits essentially no pharmacologic activity under usual doses and in the absence of opioid and/or agonistic effects of other opioid antagonists. Naloxone Injection "G.B.L." shows evidence of neither tolerance, nor physical or psychological dependence. Naloxone Injection "G.B.L." will produce withdrawal in the presence of physical dependence on opioid. The mechanism of action of Naloxone Injection "G.B.L." is not fully understood, but the preponderance of evidence suggests that Naloxone Injection "G.B.L." antagonizes opioid effects by competing for the opiate receptor sites in the CNS. Intravenous administration (I.V.) of Naloxone Injection "G.B.L." achieves the onset of action within 2 minute, while intramuscular administration (I.M) and subcutaneous administration (S.C.) is slightly less rapid to achieve the onset of action. The duration of action of Naloxone Injection "G.B.L." depends on the dose and route of administration. The subcutaneous (S.C) will take a relatively prolonged effect than intravenous (I.V.) administration. The repeated dosage of Naloxone Injection "G.B.L." depends on the dosage and the administration route of the opioid being antagonized.

Naloxone Injection "G.B.L." is rapidly distributed after intravenous administration, metabolized mainly in the liver, and excreted via urine after conjugation with glucuronide. In one study, serum half-life of Naloxone Injection "G.B.L" is 30-81 minutes (average 64±12 minutes) in adult, and 3.1±0.5 hours in neonate.

Adjunctive Use in Septic Shock

To treat septic shock patients, Naloxone Injection "G.B.L." appears to block endorphin-mediated hypotension and even in some cases to produce a rise in blood pressure and sustains for several hours, even though the mechanism of action is not completely understood. However, such rise in blood pressure does not improve patient survival. Naloxone Injection "G.B.L." is administered in early treatment for septic shock patients who react to this product. Due to limited case studies, the recommended dosage and treatment method are not determined. From published reports, the pressor effect has been shown with a single I.V. bolus injection of 0.4 mg between 3-5 minutes interval and repeat of 3-5 doses if necessary. Some studies also report I.V. bolus injection dose ranges from 0.03 mg/kg upto 0.2 mg/kg in 5 minutes. Depending on the clinical response, I.V. infusion of dose range between 0.03 mg/kg/hr and 0.3 mg/kg/hr can be administrated.

INDICATIONS

Naloxone Injection "G.B.L." is indicated for the complete or partial reversal of pharmacological effects of opioid overdosage.

USAGE

Naloxone Injection "G.B.L." is indicated for the complete or partial reversal of opioid pharmacological effects, including respiratory depression, induced by opioid including natural and synthetic narcotics, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine and butorphanol. Naloxone Injection "G.B.L." is also indicated for the diagnosis of suspected acute opioid overdosage, and can also be applied to manage hypotension induced by septic shock (see CLINICAL PHARMACOLOGY; Adjunctive Use in Septic Shock).

[According to Public Available References]

CONTRAINDICATIONS

Naloxone Injection "G.B.L." is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of other ingredients in Naloxone Injection "G.B.L.".

WARNINGS

Drug Dependence

Naloxone Injection "G.B.L." should be administered cautiously to neonates whose mothers are known or suspected to be physically dependent on opioids. An abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome in such cases. Withdrawal syndromes of patients who are know to be physically dependent on opioids include: body aches, diarrhoea, tachycardia, fever, running nose, sneeze, piloerection, sweating, yawning, nausea and vomit, nervous, unease or irritated, seizure or trembling, abdominal cramps, weak and rising blood pressure. Opiate withdrawal syndromes of neonates include cramp, excessive crying and excessive atonicity. Patients should be kept under continued surveillance shall they have satisfactory response to Naloxone Injection "G.B.L.". As the duration of action of some opioids may exceed that of Naloxone Injection "G.B.L.", patients should be administered repeated doses of Naloxone Injection "G.B.L." whenever is necessary.

Naloxone Injection "G.B.L." is not effective to treat respiratory depression caused by non-opioid drugs; for example, Naloxone Injection "G.B.L." cannot reverse respiratory depression caused by buprenorphine completely. If an incomplete response occurs, respirations should be mechanically assisted.

PRECAUTIONS

General

In addition to Naloxone Injection "G.B.L.", other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

Depression syndromes of rapid opiate-like drug reverse after surgery include nausea, vomit, sweating, trembling, tachycardia, hypertension, cramp, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Ultimately, it may lead to death. The adverse events associated with the use of Naloxone Injection "G.B.L." in postoperative patients include: hypotension, hypertension, ventricular tachycardia, ventricular fibrillation and pulmonary edema. Clinical reports show that death, coma, and encephalopathy have been the sequelae of these events. These events were found in patients with cardiovascular disease or those who derived cardiovascular adverse events after taking other medications. Although there is no evidence of relationship between Naloxone Injection "G.B.L." and these events, care should be considered when administering Naloxone Injection "G.B.L." on patients with cardiac disease, or those with hypotension, ventricular tachycardia or fibrillation, and pulmonary edema, and are taking drugs containing strong cardio toxicity. The pathology of pulmonary edema induced by Naloxone Injection "G.B.L." is generally considered similar to that of neurogenic pulmonary edema, for example, excessive catecholamine generated by central nerve system leads to mass bloods flow into pulmonary vessels and hence increases hydrostatic pressure.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no studies of carcinogenic potential of Naloxone Injection "G.B.L." in animals. As to the Mutagenesis, Naloxone Injection "G.B.L." was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test. In the in vitro study of Chinese hamster V79 cell HGPRT mutation test and the rat bone marrow chromosome aberration, there is no sign of mutagenesis. The fertility studies conducted in mice and rats at doses 50 times (10 mg/day) the human dose, showed Naloxone Injection "G.B.L." caused no impairment of fertility.

Use in Pregnancy

Teratogenic Effects: Pregnancy Category B:

There is no evidence of impaired fertility or harm to the fetus using Naloxone Injection "G.B.L." in the reproduction studies in mice and rats at doses up to 50 times (10 mg/day) the human dose. For the risk-benefit consideration, there are no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not predictive of human response, Naloxone Injection "G.B.L." should be used in pregnant women only if clearly needed.

Non-Teratogenic Effects

Caution and risk-benefit should be evaluated when administering Naloxone Injection "G.B.L." on pregnant women who are known or suspected to be opiate dependent due to the dependence of opioid of mother will also cause opiate dependence of infants.

Use in Labor and Delivery

The effect of Naloxone Injection "G.B.L." on duration of delivery is unknown.

Nursing Mothers

It is not known whether Naloxone Injection "G.B.L." is excreted in human milk. Nursing mother should take caution when using Naloxone Injection "G.B.L." as most drugs can be excreted in human milk.

Pediatric Use

Safety and effectiveness of Naloxone Injection "G.B.L." for treatment of septic shock of pediatrics and neonates are unknown.

Renal Insufficiency/Failure

There are no sufficient clinical trials to assess the safety and effectiveness of Naloxone Injection "G.B.L." in patients with renal insufficiency/failure. It should be cautious during administrating Naloxone Injection "G.B.L." to this patient group.

Liver Disease

There are no sufficient clinical trials to assess the safety and effectiveness of Naloxone Injection "G.B.L." in patients with liver disease. In a small study of patients

with liver cirrhosis, it showed that naloxone in the serum of patients with liver disease is 6 times higher than those with healthy livers. Naloxone Injection "G.B.L." has good tolerance and shows no adverse response. It should be cautious during administrating Naloxone Injection "G.B.L." to this patient group.

ADVERSE REACTIONS

Postoperative Reaction

The adverse events associated with the use of Naloxone Injection "G.B.L." in postoperative patients include: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Clinical reports show that death, coma, and encephalopathy have been the sequelae of these events. Overdosage of Naloxone Injection "G.B.L." in postoperative patients will lead to obvious pain and unrest. (Refer to PRECAUTIONS, AND DOSAGE AND ADMINISTRATION/GENERAL; USAGE/ADULTS: POSTOPERATIVE OPIOID DEPRESSION)

Opioid Suppression

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, supraventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest, which may result in death. (Refer to PRECAUTIONS).

Opioid Dependence

Patients who are physically dependent on opioids may precipitate an acute withdrawal syndrome which may include, but is not limited to, the following signs and symptoms: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal may also include: convulsions; excessive crying; hyperactive reflexes. (Refer to WARNINGS)

DRUG ABUSE AND DEPENDENCE

Naloxone Injection "G.B.L." is an opioid antagonist. Physical dependence associated with the use of Naloxone Injection "G.B.L." has not been reported. Tolerance to the opioid antagonist effect of Naloxone Injection "G.B.L." is not known to occur.

DRUG OVERDOSAGE

There is limited clinical experience with Naloxone Injection "G.B.L." overdosage in humans.

Adult Patients

In one study, healthy patients and those who are physically opiate dependent, received 24 mg/ 70 kg of naloxone hydrochloride, did not demonstrate toxicity.
In another study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m^2/min) of naloxone hydrochloride followed immediately by 2 mg/kg/hr for 24 hours. Some serious adverse events were: seizures (2 patients), severe hypertension (1 patient), and hypotension and /or bradycardia (3 patients). At doses of 2 mg/kg in normal subjects, memory decline is reported.

Pediatric Patients

Up to 11 doses of 0.2 mg of naloxone hydrochloride (2.2 mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulfate. Pediatric reports include a 2-1/2 year-old child who inadvertently received a dose of 20 mg of naloxone hydrochloride, and a 4-1/2 year-old child who received 11 doses during a 12-hour period, showed no adverse sequelae.

PATIENTS MANAGEMENT

Patients who experience a naloxone hydrochloride overdose should be treated in a closely supervised environment. Physicians should contact a poison center for the most up-to-date patient management information.

DOSAGE AND ADMINISTRATION

General

Naloxone Injection "G.B.L." is prescribed by doctors only. Naloxone Injection "G.B.L." may be administered intravenously, intramuscularly, or subcutaneously.
The most rapid onset of action is achieved by intravenous administration and is recommended in emergency situations.
Since the duration of action of some narcotics may exceed that of Naloxone Injection "G.B.L.", the patient should be kept under continued surveillance and administrated doses of Naloxone Injection "G.B.L." repeatedly as necessary.

Intravenous Infusion

For intravenous infusion, Naloxone Injection "G.B.L." can be diluted in normal saline or 5% dextrose solutions. The addition of 2 mg of Naloxone Injection "G.B.L." in 500 mL of either normal saline or 5% dextrose solution provides a concentration of 0.004 mg/mL. Mixtures should be used within 24 hours, or discarded otherwise. The rate of administration should be titrated in accordance with the patient's response. There cannot be mixture of Naloxone Injection "G.B.L." with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to Naloxone Injection "G.B.L." unless its effect on the chemical and physical stability of the solution has first been established.

GENERAL ISSUES

Naloxone Injection "G.B.L." should be checked if there is any particles or changing color before use.

USAGE

Adults

Opioid Overdose – Known or Suspected

An initial dose of 0.4 mg to 2 mg of Naloxone Injection "G.B.L." may be administered intravenously. Repetition at a 2 to 3 minute intervals may be applied if the desired degree of counteraction and improvement in respiratory functions is not obtained. If no response is observed after 10 mg of Naloxone Injection "G.B.L." have been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Opioid Depression

Smaller doses of Naloxone Injection "G.B.L." are usually sufficient for the partial reversal of opioid suppression following the use of opioids during surgery. The dose of Naloxone Injection "G.B.L." should be titrated according to the patient's response. For the initial reversal of respiratory depression, increments of 0.1 to 0.2 mg should be injected intravenously at 2 to 3 minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of Naloxone Injection "G.B.L." may result in significant reversal of analgesia, coming around pain and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, and sweating or circulatory stress. Repeat doses of Naloxone Injection "G.B.L." may be required within 1 to2 hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of an opioid. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

Septic Shock

The optimal dosage of Naloxone Injection "G.B.L." or duration of therapy for the treatment of hypotension in septic shock patients has not been established (see **CLINICAL PHARMACOLOGY**).

Children

Opioid Overdose – Known or Suspected

The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, Naloxone Injection "G.B.L." may be administered I.M. or S.C. in divided doses. If necessary, Naloxone Injection "G.B.L." can be diluted with sterile water for injection.

Neonates

Opioid-induced Depression

The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. Please refer to Adult Postoperative Depression for repeated administration.

HOW SUPPLIED:

Naloxone Injection "G.B.L." is available as following:
0.4 mg/ml 1 ml/ampule, 10 ampules/box

Store at controlled room temperature below 25°C.
Keep out of reach of children. Prevent from light.

Manufactured for: Uni Pharma Co. Ltd.
8F, No. 43, Lane 115, Sec.2, Chung Shan N. Rd.,
Taipei, Taiwan, R.O.C. 10448
Manufactured by: Genovate Biotechnology Co., Ltd.
No.1, First Industrial Road, Hsin-Chu Expanded Industrial Park,
Hsin-Chu, Taiwan, R.O.C. 30351

Printed in Taiwan Naloxone.02HK-E V01. 20080831