MORPHINE HYDROCHLORIDE מורפין הידרוכלוריד

INJECTION להזרקה תת עורית, לתוך השריר או לתוך הוריד

Narcotic prescription required.

Composition

Each ampoule of 1 ml contains:

Active Ingredient

Morphine hydrochloride 10 mg or 20 mg

Other Ingredients

Sodium metabisulfite (as a preservative), hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injection.

Mechanism of Action

Morphine is a powerful narcotic analgesic.

Indications

Symptomatic relief of moderate to severe pain, especially that associated with neoplastic disease, myocardial infarction, and surgery.

Pre-operatively as an adjunct to anesthesia for pain relief and to allay anxiety.

Alleviation of the anxiety associated with severe pain. It is useful as a hypnotic where sleeplessness is due to pain.

Relief of pain due to biliary or renal colic.

Contraindications

Known hypersensitivity to any ingredient of the preparation, or to other opiates.

Morphine should not be administered to patients with respiratory depression or obstructive airways disease, especially in the presence of cyanosis and excessive bronchial secretion, and following surgery of the biliary tract.

Morphine is contraindicated in patients who are receiving monoamine oxidase inhibitors or those who have recently received such agents. Therapeutic doses of morphine have occasionally precipitated unpredictable, severe, and sometimes fatal reactions in patients who have received monoamine oxidize inhibitors within the last 14 days. The mechanism of these reactions is unclear, but may be related to a preexisting hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute narcotic overdose. In other reactions, the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia and hypertension.

Morphine is contraindicated in acute alcoholism, head injuries, conditions in which intracranial pressure is raised, delirium tremens, convulsive disorders, acute bronchial asthma and heart failure secondary to chronic lung disease.

Morphine is contraindicated in any patient who has or is suspected of having a paralytic ileus.

Morphine is usually not recommended for use in infants under 1 year of age.

Morphine is contraindicated in premature infants or during labor for delivery of a premature infant.

Morphine contraindicated in case of diarrhea caused by poisoning, until the toxic material has been eliminated from the gastrointestinal tract, or diarrhea associated with *Pseudomembranous colitis* caused by antibiotics.

Warnings

***This preparation contains a preservative. Therefore, it should not be used for intrathecal or epidural injection*.**

Morphine Injection contains sodium metabisulfite as a preservative. As with other sulfites, sodium metabisulfite may cause allergic-type reactions in certain susceptible patients, including anaphylactic symptoms and life-threatening, or less severe, asthmatic episodes. The overall prevalence of sulfite sensitivity in the general population is unknown, and probably low. Sulfite sensitivity is seen more frequently in asthmatic rather than in nonasthmatic patients.

Morphine administration should be limited to use by those familiar with the management of respiratory depression.

Facilities where morphine is administered must be equipped with resuscitative equipment, oxygen, naloxone injection, and other resuscitative drugs.

Intravenous Use

Morphine may be administered intravenously, but the injection should be given very slowly, preferably in the form of a diluted solution. Administration should only be performed when a narcotic antagonist and facilities for assisted or controlled respiration are immediately available. When morphine is administered parenterally, especially intravenously, the patient should be lying down.

Rapid I.V. injection of narcotic analgesics, including morphine, increases the incidence of adverse reactions such as severe respiratory depression, apnea, hypotension, peripheral circulatory collapse and cardiac arrest.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of morphine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, morphine must be used with extreme caution, and only when deemed essential.

Asthma and Other Respiratory Conditions

Morphine should be used with extreme caution in patients undergoing an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, and patients with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even unusual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypertensive Effect

The administration of morphine may result in severe hypotension in postoperative patients or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or the concurrent administration of drugs such as the phenothiazines or certain anesthetics.

Morphine, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Drug Dependence

Repeated administration of morphine may induce tolerance to the drug. This may create a tendency to increase dosage requirements in order to obtain the desired effect, or to physical and psychological dependence with the development of withdrawal symptoms after abrupt cessation of therapy.

A withdrawal syndrome can be avoided by gradually reducing the dose as the pain requirements lessen. Tolerance and drug dependence are unusual after opioid administration in the setting of acute pain, e.g., postoperative pain. Psychological dependence or addiction (compulsive drug use characterized by a continued craving for an opioid and the need to use the opioid for effects other than pain relief), occurs in less than 0.03% of patients.

Other

Cross-tolerance between narcotic analgesics can occur.

Use in Pregnancy

Safety of use in pregnancy has not been established.

The placental transfer of opioids is rapid.

Maternal addiction following illicit use, resulting in withdrawal symptoms in the neonate, is well documented. Withdrawal symptoms include irritability, excessive crying, yawning, sneezing, increased respiratory rate, tremors, hyperreflexia, fever, vomiting, increased stools and diarrhea. These symptoms usually appear during the first days of life.

Morphine should therefore be given to pregnant women only if clearly needed. Morphine should not be used in pregnant women prior to the labor period unless the potential benefits outweigh the possible hazards, because safe use in pregnancy prior to labor has not been established relative to possible adverse effects on fetal development.

Use in Labor and Delivery

The use of morphine in obstetrics may reduce the strength, duration and frequency of uterine contractions resulting in prolonged labor. It passes the placental barrier and may produce depression of respiration in the newborn. In resuscitation and severe depression, the administration of a narcotic antagonist such as naloxone or nalorphine may be required. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate.

Morphine is contraindicated during labor for delivery of a premature infant (see Contraindications).

Use in Lactation

Morphine is secreted in breast milk. Therefore, mothers receiving this medication should not nurse.

Use in Pediatrics

Safety and effectiveness have not been established.

Morphine is contraindicated for use in premature infants (see Contraindications).

Use in the Elderly

Morphine should be used with caution in the eldery. Dosage should be carefully controlled and the patient monitored for possible drug interactions. A lower dosage than usual may be necessary because some elderly patients are highly sensitive to the respiratory depressant effect of morphine.

In addition, geriatric patients are more likely to have prostatic hypertrophy or renal function impairment, and therefore may be more adversely affected by urinary retention. Therefore, lower doses or longer dosing intervals than those usually recommended for adults may be required, and are usually therapeutically effective, for these patients.

Adverse Reactions

As with other narcotic analgesics, the major hazards of morphine are respiratory depression, apnea and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred.

Naloxone injection and resuscitative equipment should be immediately available for administration in case of life-threatening or intolerable side effects.

Because of a delay in maximum CNS effects with intravenously administered drug (30 minutes), rapid administration may result in overdosing.

The most frequently observed adverse reactions include lightheadedness (especially in ambulatory patients), dizziness, and sedation, nausea, vomiting and sweating.

Some adverse reactions in ambulatory patients may be alleviated by lying down.

Other adverse reactions are listed below:

Central Nervous System

Euphoria, dysphoria, delirium, insomnia, agitation, anxiety, fear, hallucinations, disorientation, confusion, lethargy, impairment of mental and physical performance, coma, mood changes, weakness, headache, visual disturbances, tremor, psychic dependence and miosis. Convulsions or myoclonus may rarely occur when high doses of morphine are given I.V. or intraspinally.

Gastrointestinal

Dry mouth, anorexia, constipation, biliary tract spasm.

Patients with chronic ulcerative colitis may experience increased colonic motility. Toxic dilatation has been reported in patients with acute ulcerative colitis.

Cardiovascular

Facial flushing, hypotension (more frequent), hypertension, peripheral circulatory collapse, tachycardia, bradycardia, arrhythmia, palpitations, chest wall rigidity and syncope. While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines.

Allergic

Urticaria, other skin rashes, diaphoresis, laryngospasm, edema, and rarely hemorrhagic urticaria.

A case of thrombocytopenia induced by morphine has been reported. Wheals, phlebitis and pain may occur at the site of I.V. injection.

Effects induced by histamine release e.g., decreased blood pressure, fast heartbeat, increased sweating, redness or flushing of the face, wheezing or troubled breathing.

Genitourinary

Urinary retention or hesitance, anti-diuretic effect, and reduced libido and/or potency.

Other

Pain at the injection site.

In general, side effects are amenable to reversal by narcotic antagonists.

Patients experiencing these adverse reactions should receive lower doses of the drug and/or symptomatic treatment of the side effect (e.g. laxatives for constipation). During chronic opioid use, tolerance develops to many of the side effects, which gradually subside. In general, side effects of morphine are amenable to reversal by narcotic antagonists, but should be used only after careful consideration of the risks.

Precautions

Morphine should always be administered with caution, and in reduced dosage, to elderly and debilitated patients, and patients with head injuries, severe hepatic or renal impairment, biliary tract disorders, cardiovascular disease, delirium, tremens, cerebral arteriosclerosis, fever, toxic psychosis, severe CNS depression, coma, hypothyroidism, adrenocortical insufficiency, shock, prostatic hypertrophy, urethral stricture or Addison's disease, or a history of drug abuse.

Caution is also required in patients exhibiting acute alcoholism, raised intracranial pressure, obstructive bowel disorders, myasthenia gravis or convulsive disorders.

Morphine, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Morphine should be used with extreme caution in patients with disorders characterized by hypoxia, since even usual therapeutic doses of narcotics may decrease respiratory drive to the point of apnea, while simultaneously increasing airway resistance. Care is also urged in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis).

Supraventricular Tachycardia

Morphine should be used with caution in patients with atrial flutter and other supraventricular tachycardias, because of a possible vagolytic action which may produce a significant increase in the ventricular response rate.

Acute Abdominal Conditions

As with other narcotics, morphine may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Cardiovascular

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be observed carefully for orthostatic hypotension, particularly in transport.

Asthma and Other Respiratory Conditions

Patients with chronic obstructive pulmonary disease and asthmatic attack may develop acute respiratory failure with administration of morphine. Use in these patients should be reserved for those whose conditions require endotracheal intubation and respiratory support or control of ventilation.

Convulsions

Morphine may aggravate preexisting convulsions in patients with convulsive disorders.

Convulsions may occur in individuals without a history of convulsive disorders, following use of a higher than recommended dosage.

Kidney or Liver Dysfunction

Morphine may have a prolonged duration and cumulative effect in patients with reduced metabolic rates and hepatic or renal dysfunction. Therefore, care should be exercised in administering morphine in these conditions, particularly with repeated dosing.

Patients may experience drowsiness while receiving morphine, and should therefore be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving a car or operating machinery. The same precaution applies to childhood activities such as bicycle riding or playing near traffic.

Drug Interactions

***Morphine/ Other CNS Depressants (including Alcohol)/ Anesthetics/Phenothiazines/ Anticholinergics/Neuromuscular Blocking Agents*:** The effect of morphine may be potentiated by concurrent administration with other central nervous system depressants such as sedatives, antihistaminics, alcohol, anticholinergics, neuromuscular blocking agents or psychotropic drugs (e.g. phenothiazines, butyrophenones and tricyclic antidepressants).

Premedication or intra-anesthetic use of neuroleptics with morphine may increase the risk of respiratory depression.

Concomitant administration of morphine with phenothiazines may induce severe hypotension. Patients should be instructed to avoid alcohol while under treatment, since the individual response cannot be foreseen.

***Morphine/ Monoamine Oxidase Inhibitors**:* See Contraindications.

Morphine/Zidovudine: Because morphine may decrease the clearance of zidovudine, concurrent use should be avoided because the toxicity of either or both of these medications may be potentiated.

Opioid Analgesics/Opioid Antagonist/Mixed Agonist-Antagonist Opioid Analgesics: Administration of an opioid antagonist such as naloxone or naltrexone will block the therapeutic effect of morphine, and will precipitate withdrawal symptoms in patients physically dependent on opioids; such symptoms may persist for up to 48 hours and be difficult to reverse. Similarly, administration of a mixed agonist/antagonist opioid analgesic (e.g., pentazocine, buprenorphine) to a patient receiving therapy with a pure agonist opioid such as morphine may reduce the analgesic effect, or precipitate withdrawal.

Opioid Analgesics/Antidiarrheals: Concurrent use of opioid analgesics with antidiarrheals may increase the risk of severe constipation, as well as CNS depression.

Opioid Analgesics/Antihypertensives: Patients receiving concurrent antihypertensive medication and opioid analgesics, including morphine, should be monitored closely, due to the increased risk of orthostatic hypotension.

Opioid Analgesics/Cimetidine: Case reports have described CNS toxicity (confusion, disorientation, respiratory depression, apnea, seizures) following concurrent administration of cimetidine and opioid analgesics, though no clear-cut cause and effect relationship has been established.

Diagnostic Interference

Narcotic analgesics may produce increases in plasma amylase and plasma lipase levels; the diagnostic utility of determinations of these enzymes may be compromised for up to 24 hours after the medication has been administered.

Dosage and Administration

***This preparation contains a preservative. Therefore, it should not be used for intrathecal or epidural injection*.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Morphine Injection is intended for intramuscular, intravenous and subcutaneous administration.

Notes:

1. Resuscitative equipment and medications, including a specific antagonist (naloxone HCl injection) should be immediately available for management of respiratory depression or other complications that may arise from inadvertent morphine intravascular administration. Also, facilities for adequate monitoring of the patient's respiratory status must be available for 24 hours after each dose since delayed respiratory depression may occur.
2. Rapid I.V. injection of most opioid analgesics has caused chest wall rigidity, anaphylactoid reactions, severe respiratory depression, hypotension, peripheral circulatory collapse and cardiac arrest. It is recommended that when an opioid analgesic must be given intravenously, dosage should be reduced and a dilute solution should be injected slowly over a period of several minutes.
   The patient usually should be lying down and should remain recumbent for a period of time to minimize side effects such as hypotension, dizziness, lightheadedness, nausea and vomiting. If these side effects occur in an ambulatory patient, they may be relieved if the patient lies down. An opioid antagonist and equipment for artificial ventilation should be available.

Subcutaneous or Intramuscular Injection

Adults

The usual dose by subcutaneous or intramuscular injection is 5-20 mg every 4 hours.

Children

Up to 1 month of age	150 mcg / kg body weight
1 to12 months of age	200 mcg/ kg body weight
1 to 5 years of age	2.5- 5 mg
6 to 12 years of age	5-10 mg.

Intravenous Injection

Doses of up to 15 mg have been given by slow intravenous injection, sometimes as a loading dose for continuous or patient-controlled infusion.

Overdosage

Manifestations

Signs of overdosage include pin-point pupils, depressed respiration, and coma. In severe poisoning there may be dilation of the pupils, shock, severe respiratory depression and pulmonary edema, circulatory collapse and cardiac arrest.

Treatment

Intensive supportive therapy should be carried out. Naloxone is a recommended antidote, 400 mcg of naloxone hydrochloride should be administered S.C., I.M. or I.V., and repeated at intervals of 2-3 minutes if necessary. In children a dose of 5-10 mcg/kg body weight may be administered. In neonates a dose of 10 mcg/kg body weight may be administered.

If naloxone is not available, nalorphine hydrobromide may be administered I.V. in doses of 5-10 mg, and if necessary, repeated every 15 minutes, up to a total of 40 mg. In severe poisoning, a single dose of 40 mg may be administered.

Alternatively, 1 mg of levallorphan tartrate may be administered I.V, followed if necessary by 1 or 2 doses each of 500 mcg.

In individuals who are physically dependent upon morphine, the administration of the usual dose of naloxone will precipitate an acute withdrawal syndrome. The severity of the syndrome is dependent upon the degree of physical dependence and the dose of naloxone given. If at all possible, the use of an antagonist should be avoided in such individuals. However, if absolutely necessary, the naloxone should be administered with extreme caution, using only 10-20% of the usual initial dose given. When naloxone is used to reverse postoperative opioid depression, particular caution should be exercised in cardiac patients.

Supportive measures should be employed. The patient should be observed for a rise in temperature or pulmonary complications that may require antibiotic therapy.

Drug Registration No.:

Morphine Hydrochloride 10 mg: 36.932.2650
Morphine Hydrochloride 20 mg: 36.942.2649

Manufacturer

Biogal Pharmaceutical Works Ltd,
Debrecen, Hungary Teva Group

License Holder

Teva Pharmaceutical Works Ltd.,
P.O.Box 3190, Petach Tikva.