PRESCRIBING INFORMATION

®MORPHINE LP EPIDURAL

Morphine Sulfate Injection USP

0.5 mg/mL and 1 mg/mL

Opioid Analgesic
©MORPHINE LP EPIDURAL

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0.5 mg/mL and 1 mg/mL

Opioid Analgesic

Isotonic
Preservative and Sulfite Free

DELAYED RESPIRATORY DEPRESSION WARNING

SEVERE POTENTIALLY FATAL RESPIRATORY DEPRESSION MAY OCCUR UP TO 24 HOURS FOLLOWING EPIDURAL ADMINISTRATION OF MORPHINE. THEREFORE, PATIENTS WHO RECEIVE EPIDURAL MORPHINE SHOULD BE KEPT UNDER CONSTANT OBSERVATION IN A SETTING EQUIPPED FOR RESUSCITATION FOR AT LEAST 24 HOURS AFTER THEIR LAST INJECTION. EPIDURAL ADMINISTRATION OF MORPHINE SHOULD BE UNDERTAKEN ONLY UNDER THESE CONDITIONS.

ACTION AND CLINICAL PHARMACOLOGY

Morphine exerts its primary effects on the central nervous system and organs containing smooth muscle. Pharmacologic effects include analgesia, drowsiness, alteration in mood (euphoria), reduction in body temperature (at low doses), dose-related depression of respiration, interference with adrenocortical response to stress (at high doses), reduction in peripheral resistance with little or no effect on cardiac index.

Administration of morphine by the epidural route minimizes the central effects of systemic morphine, i.e. sedation. Autonomic reflexes are not affected by epidural morphine; however, it exerts spasmogenic effects on the gastrointestinal tract that result in decreased peristaltic activity. The delay in the onset of analgesia following epidural injection may be attributed to its relatively poor lipid solubility and its slow access to the receptor sites. The hydrophilic character of morphine may also explain its retention in the CSF and its slow release into the systemic circulation, resulting in a prolonged effect. Morphine, as with other opioids, acts on receptors in the brain, spinal cord and other tissues. Its action is predominantly on the μ receptor.

Nausea and vomiting with epidural morphine may be prominent and are thought to be the result of central stimulation of the chemoreceptor trigger zone. Histamine release is common; allergic manifestations of urticaria and, rarely, anaphylaxis may occur. Bronchoconstriction may occur either as an idiosyncratic reaction or from large doses.

Although prolonged analgesia may be achieved with single doses of epidural morphine, extreme caution is required regarding possible adverse reactions, particularly potentially fatal, delayed respiratory depression (see WARNINGS).
Peak serum levels following epidural administration of Morphine LP Epidural (Morphine Sulfate Injection USP) are reached within 30 minutes in most subjects and decline to very low levels during the next 2 to 4 hours. The onset of action occurs in 15 to 60 minutes following epidural administration; analgesia may last up to 24 hours.

INDICATIONS AND CLINICAL USE

Morphine LP Epidural (Morphine Sulfate Injection USP) is a preservative free solution which may be administered by bolus epidural injection.

Epidural administration of morphine has been useful in the management of intractable pain of malignant disease and following major surgery or trauma in some patients.

CONTRAINDICATIONS

Hypersensitivity to morphine or other opioids, respiratory insufficiency or depression, severe CNS depression, attack of bronchial asthma, heart failure secondary to chronic lung disease, cardiac arrhythmias, increased intracranial or cerebrospinal pressure, head injuries, brain tumour, acute alcoholism, delirium tremens, convulsive disorders, after biliary tract surgery, suspected surgical abdomen, surgical anastomosis, concomitantly with MAO inhibitors or within 14 days of such treatment.

Administration of morphine by the epidural route is contraindicated in conjunction with anticoagulant therapy, bleeding diathesis, parenterally administered corticosteroids within the preceding two-week period, or other concomitant drug therapy or medical conditions which would contraindicate the technique of epidural administration.

WARNINGS

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Morphine can produce drug dependence and therefore has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of morphine.
Morphine should be used with caution and in reduced dosage in patients who are concurrently receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension and profound sedation or coma may result.

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, opioids 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 if its use is deemed essential.

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

Morphine should not be used in pregnant women prior to the labour period unless the potential benefits outweigh the possible hazards because safe use in pregnancy prior to labour has not been established relative to possible adverse effects on fetal development.

**PRECAUTIONS**

Extreme caution should be exercised when administering epidural morphine, since inadvertent intrathecal injection will increase the risk of respiratory depression (see WARNINGS).

Patients with chronic pain due to cancer develop a tolerance for opioids and, therefore, the risk of delayed respiratory depression may be decreased.

Smooth muscle hypertonicity may result in biliary colic, difficulty in urination and possible urinary retention requiring catheterization. Consideration should be given to the risks inherent in urethral catheterization, e.g. sepsis, when epidural administration is considered, especially in the perioperative period.

Thoracic administration has been shown to increase the incidence of early and late respiratory depression even at doses of 1 to 2 mg.

**Drug Abuse and Dependence**

Cerebral and spinal receptors may develop tolerance/dependence independently, as a function of local dosage. Care must be taken to avert withdrawal in those patients who have been maintained on parenteral/oral opioids when epidural administration is considered. Withdrawal may occur following chronic epidural administration, as well as the development of tolerance to morphine by these routes.
Patients with Special Diseases and Conditions
Morphine should be administered with caution in aged or debilitated patients, in Addison’s disease, in the presence of increased intracranial/intraocular pressure, severe impairment of hepatic or renal function, hypothyroidism, prostatic hypertrophy or urethral stricture and in patients with head injury. Pupillary changes (miosis) may obscure the course of intracranial pathology. Extreme care is urged in patients who have a decreased respiratory reserve (such as emphysema, severe obesity, kyphoscoliosis, or chronic obstructive pulmonary disease). Administration of morphine may result in acute respiratory failure in these patients, and should not be undertaken in the absence of respiratory support and control of ventilation. Seizures may result from high doses. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

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

Acute Abdominal Condition
The administration of morphine or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

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

Supraventricular Tachycardia
Because of possible vagolytic action that may produce a significant increase in the ventricular response rate, morphine should be used with caution in patients with atrial flutter and other supraventricular tachycardias.

Convulsions
Morphine may aggravate preexisting convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders.

Kidney or Liver Dysfunction
Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Hence, care should be exercised in administering morphine in these conditions, particularly with repeated dosing.

Information for the Patient
Morphine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Morphine, in combination with other opioid analgesics, phenothiazines, sedative/hypnotics, and alcohol, has additive depressant effects. Patients should be cautioned accordingly.
Carcinogenesis, Mutagenesis
Morphine has no known carcinogenic or mutagenic potential. However, no long term animal studies are available to support this observation.

Drug Interactions
Depressant effects of morphine are potentiated by other CNS depressants such as alcohol, sedatives, antihistaminics or psychotropic drugs (e.g. MAO inhibitors, phenothiazines, butyrophenones and tricyclic antidepressants). Use of neuroleptics as premedication or during anesthesia might increase the risk of respiratory depression.

Use in Children
Safety and efficacy of epidural morphine in children have not been established.

Use in Pregnancy
Animal reproduction studies in pregnant mice receiving 0.4 to 40 mg/mL morphine sulfate via an infusion pump resulted in a significant reduction in mean fetal weight and an increase in the total number of soft tissues and/or skeletal defects. In rats receiving 35 and 50 mg/kg/day morphine sulfate, the pregnancy rate was reduced. In the surviving fetuses, the growth rate was reduced and the mortality rate was significantly higher.

There have been no well-controlled studies on the safety and efficacy of epidural morphine administration in pregnant women. Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms. Therefore, morphine sulfate should be given to a pregnant woman only if clearly needed.

Use in Obstetrics
The use of morphine in obstetrics may prolong labor. It crosses the placental barrier and may produce respiratory depression in the newborn. For resuscitation and in severe depression, the administration of an opiate antagonist such as naloxone or nalorphine may be required.

Controlled clinical studies have shown that epidural administration has little or no effect on the relief of labour pain.

Nursing Women
Morphine appears in the milk of nursing mothers. Caution should be exercised when it is administered to a nursing mother.

ADVERSE REACTIONS

General
The major hazards of morphine and of other opioid analgesics are respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest. The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, constipation and sweating. These effects seem to be more prominent in ambulatory
patients and in those who are not suffering severe pain. In such individuals, lower doses may be advisable. Some adverse reactions may be alleviated in the ambulatory patient if he lies down.

Following bolus administration by the epidural route, morphine may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centres in the brain. Late (up to 24 hours) onset of acute respiratory depression has been reported with administration by the epidural route and is believed to be the result of rostral spread. This depression may be severe and could require intervention (see WARNINGS). Even without clinical evidence of ventilatory inadequacy, a diminished CO₂ ventilation response may be noted for up to 22 hours following epidural administration.

Epidural administration is accompanied by a high incidence (approximately 40%) of pruritus which is dose-related but not confined to the site of administration. Nausea and vomiting are frequently seen in patients (approximately 50% and 25%, respectively) following morphine administration. Urinary retention, which may persist for 10 to 20 hours following single epidural administration, has been reported in up to 90% of males. The incidence is somewhat lower in females. Catheterization may be required (see PRECAUTIONS).

Other adverse reactions include the following

Central Nervous System
Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastrointestinal
Dry mouth, anorexia, constipation, and biliary tract spasm.

Cardiovascular
Flushing of the face, bradycardia, palpitation, faintness and syncope.

Genitourinary
Urinary retention or hesitance, antidiuretic effect and reduced libido and/or potency.

Allergic
Pruritus, urticaria, other skin rashes, edema, and rarely hemorrhagic urticaria.

In general, side effects are amenable to reversal by opioid antagonists. Naloxone injection and resuscitative equipment should be immediately available for administration in case of life-threatening or intolerable side effects.
REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

Symptoms
Overdosage is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis) with or without concomitant CNS depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, miosis, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment
Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The opiate antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids. Therefore, an appropriate dose of this antagonist should be administered preferably by the IV route, simultaneously with assisted respiration.

Following epidural morphine overdose, naloxone (usually 0.4 mg) should be administered IV, simultaneously with respiratory resuscitation. As the duration of effect of naloxone is considerably shorter than that of epidural morphine, repeated administration may be necessary. Patients should be closely observed for evidence of renarcotization.

Onset of respiratory depression may be delayed up to 24 hours following epidural administration. In painful conditions, reversal of opioid effect may result in acute onset of pain. Careful administration of naloxone in incremental doses may permit reversal of side effects without completely reversing analgesia.
An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

In an individual physically dependent on opioids, the administration of the usual dose of opiate antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opiate antagonists in such individuals should be administered with extreme care and about 10 to 20% of the usual initial dose administered.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

**DOSAGE AND ADMINISTRATION**

*(Before using, see WARNINGS)*

Morphine LP Epidural should be administered epidurally by physicians experienced in the techniques of epidural administration and who are thoroughly familiar with the labelling.

**Epidural Administration**

Proper placement of the needle or catheter in the epidural space, using appropriate sterile technique, should be verified before each Morphine LP Epidural injection. Acceptable techniques for verifying proper placement include: a) aspiration to check for absence of blood or cerebrospinal fluid, or b) administration of 5 mL (3 mL in obstetric patients) of 1.5% unpreserved lidocaine and epinephrine (1:200 000) injection, and then observing the patient for lack of tachycardia (indicating that vascular injection has not been made) and lack of sudden onset of spinal anesthesia with motor paresis in the legs (indicating that intrathecal injection has not been made).

**Epidural Adult Dosage**

Onset of analgesia following epidural administration of 5 mg of Morphine LP Epidural generally occurs in 15 to 60 minutes and may last up to 24 hours. The lumbar region is the recommended site of administration. Thoracic administration has been shown to increase the incidence of early and late respiratory depression.

Initial bolus of 5 mg in the lumbar region may provide satisfactory pain relief for up to 24 hours. If adequate pain relief is not achieved within 1 hour, careful administration of incremental doses of 1 to 2 mg at intervals sufficient to assess effectiveness may be given through an in-dwelling catheter. In the event of continued inadequate analgesia, re-verification of catheter placement should be made by repeat injection of a test dose of lidocaine and epinephrine (see above).

In patients of average build and weight, a single dose of 5 mg usually provides satisfactory relief for up to 24 hours. Further doses may be titrated in 3 to 5 mg aliquots for pain associated with
upper abdominal and thoracic procedures. For thoracic pain relief, the patient may require repeat (2 or 3) injections.

**Aged or Debilitated Patients**
Administer with caution. Doses of less than 5 mg may provide satisfactory pain relief for up to 24 hours.

**Repeat Dosage**
If pain recurs, Morphine LP Epidural may again be administered after at least 3 to 6 hours have elapsed, depending on operation, operative site or chronic pain usage. Reduced dosage should be considered for this readministration, since the risk of respiratory depression is increased. If pain relief remains unsatisfactory, consideration should be given to alternative methods of pain control, such as systemic opioids. Cautious dosage and 24 hour observation for respiratory depression are mandatory under these conditions.

**Epidural Pediatric Use**
No information on use in pediatric patients is available.

**Morphine Dosage Reduction**
During the first two to three days of effective pain relief, the patient may sleep for many hours. This can be misinterpreted as the effect of excessive analgesic dosing rather than the first sign of relief in a pain exhausted patient. The dose, therefore, should be maintained for about 3 days before reduction, if respiratory activity and other vital signs are adequate. Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Lower doses or complete discontinuation of the opioid analgesic may become feasible due to a physiological change or the improved mental state of the patient.

**Opioid Analgesic Equivalences**
For patients who are receiving an alternate opioid, the “oral morphine sulfate equivalent” of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily morphine sulfate dosage that should provide equivalent analgesia.
Table 1 - Opioid Analgesics: Approximate Analgesic Equivalences (1)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Equivalent Dose (mg) (2) (compared to morphine 10 mg IM)</th>
<th>Duration of Action (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parenteral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Strong Opioid Agonists:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine (single dose)</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Morphine (chronic dose)</td>
<td>10</td>
<td>20 - 30 (3)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5 - 2</td>
<td>6 - 7.5</td>
</tr>
<tr>
<td>Anileridine</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Meperidine (4)</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1.5</td>
<td>5 (rectal)</td>
</tr>
<tr>
<td>Methadone (5)</td>
<td>5 - 8</td>
<td>10 - 15</td>
</tr>
<tr>
<td><strong>Weak Opioid Agonists:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>120</td>
<td>200</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5 - 10</td>
<td>10 - 15</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td><strong>Mixed Agonist-Antagonists</strong> (6):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentazocine (4)</td>
<td>60</td>
<td>180</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>10</td>
<td>3 - 6</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

(1) References:

(2) Most of these data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain.

(3) For acute pain, the oral dose of morphine is six times the injectable dose. However, for chronic dosing, this ratio becomes 2 or 3:1, possibly due to the accumulation of active metabolites.

(4) These drugs are not recommended for the management of chronic pain.

(5) Extremely variable equianalgesic dose. Patients should undergo personalized titration starting at an equivalent to 1/10 of the morphine dose.

(6) Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.
DOSAGE FORMS, COMPOSITION AND PACKAGING

Morphine LP Epidural (Morphine Sulfate Injection USP) is a sterile, isotonic solution free of antioxidants or preservatives and is an opioid analgesic intended for epidural administration.

Morphine LP Epidural is available in 0.5 mg/mL and 1 mg/mL strengths.

Each mL of Morphine LP Epidural contains either 0.5 mg or 1 mg of morphine sulfate pentahydrate, sodium chloride 9 mg for isotonicity, sulfuric acid and/or sodium hydroxide to adjust pH, and water for injection.

The 0.5 mg/mL strength is available in single use vials of 10 mL, boxes of 5.

The 1 mg/mL strength is available in single use vials of 5 mL, boxes of 5.

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from light. Discard unused portion. Do not autoclave.

NOTICE: This product has a potential for being abused.

LATEX-FREE STOPPER – Stopper contains no dry natural rubber.