

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^NMorphine-EPD
(Morphine Sulfate Injection, USP)

0.5 mg/mL and 1 mg/mL

Sterile Solution

For Epidural Use Only

Preservative-Free

Narcotic Analgesic

Hospira Healthcare Corporation
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Epidural	Sterile solution 0.5 mg/mL 1 mg/mL	Hydrochloric acid, sodium chloride, sodium hydroxide, water for injection

INDICATIONS AND CLINICAL USE

Adults

Morphine-EPD is indicated for administration by the epidural route. Although the clinical use of spinal opiates is still uncertain, epidural morphine can be useful for the relief of severe, acute pain patients who are poorly controlled by standard methods. It has also been found to be of value in the management of some patients with intractable pain of malignant disease, and following major surgery or trauma.

Morphine-EPD is not indicated as an as-needed (prn) analgesic.

Geriatrics (> 65 years of age)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

Pediatrics (< 18 years of age)

The safety and efficacy of Morphine-EPD has not been studied in the pediatric population. Therefore the use of Morphine-EPD is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance morphine sulfate or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale. Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- The administration of morphine by epidural route is also contraindicated in the presence of infection at the injection site, anticoagulant therapy, bleeding diathesis, parenterally administered corticosteroids within the preceding two-week period, other concomitant drug therapy or medical conditions which would contraindicate the technique of epidural analgesia.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, Morphine-EPD (morphine sulfate injection) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

Morphine-EPD poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Morphine-EPD, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS, Abuse and Misuse). Morphine-EPD should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of Morphine-EPD. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Morphine-EPD or following a dose

SERIOUS WARNINGS AND PRECAUTIONS

increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Morphine-EPD should be administered only in settings where adequate patient monitoring is possible. Resuscitative equipment and a specific antagonist (naloxone hydrochloride injection) should be immediately available for the management of respiratory depression as well as complications which might result from inadvertent intrathecal or intravascular injection. 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.

Accidental Exposure

Accidental exposure of even one dose of Morphine-EPD, especially by children, can result in a fatal overdose of morphine sulfate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of Morphine-EPD during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)).

Interaction with Alcohol

Caution should be observed when administering morphine to patients who have been or are taking alcohol. Morphine-EPD should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- Reserve concomitant prescribing of Morphine-EPD and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

General

It is recommended that administration of Preservative-Free Morphine-EPD (morphine sulfate injection) by epidural route be limited to the lumbar area. Thoracic administration has been

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

Extreme caution should be exercised when administering Preservative-Free Morphine-EPD since inadvertent intrathecal injection will increase the risk of respiratory depression (see **DOSAGE and ADMINISTRATION**). Patients, however, with chronic pain due to cancer develop a tolerance for narcotics 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.

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

An increased incidence of facial pruritus and reports of Type 1 Herpes Simplex have been observed in post-partum patients following epidural administration of morphine. A cause and effect relationship has not been demonstrated.

Morphine-EPD should be stored securely to avoid theft or misuse.

Morphine-EPD should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking Morphine-EPD as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of morphine sulfate can occur at particularly high doses. A morphine sulfate dose reduction or change in opioid may be required.

Abuse and Misuse

Like all opioids, Morphine-EPD is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Morphine-EPD should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Morphine-EPD, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Carcinogenesis and Mutagenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic or the mutagenic potential of morphine. No long-term follow-up studies of patients receiving morphine epidurally have been conducted

Cardiovascular

Morphine sulfate administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. Morphine sulfate may produce orthostatic hypotension in ambulatory patients. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Morphine-EPD.

The use of Morphine-EPD in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see **DOSAGE AND ADMINISTRATION**).

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Morphine-EPD and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, goosebumps, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and Adjustment or Reduction of Dosage**).

Use in Drug and Alcohol Addiction

Morphine-EPD is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Morphine-EPD; extreme caution and awareness are warranted to mitigate the risk.

Endocrine

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more

often following greater than one 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.

Gastrointestinal Effects

Morphine sulfate and other morphine-like opioids have been shown to decrease bowel motility. Morphine sulfate may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Morphine-EPD is not recommended to be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the risks. If Morphine-EPD was used during pregnancy, special attention to NOWS is warranted.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Morphine sulfate should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

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 **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 Morphine-EPD 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 **DRUG INTERACTIONS**).

Morphine-EPD should not be administered if patients have been or are consuming alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS; ADVERSE REACTIONS, Sedation; and DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Seizures may result from high doses. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

Head Injury: The respiratory depressant effects of morphine sulfate, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, morphine sulfate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, morphine sulfate must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS**).

Serotonin Syndrome: Morphine-EPD could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Morphine-EPD should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Peri-Operative Considerations

Morphine-EPD is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Morphine-EPD for at least 24 hours before the operation and Morphine-EPD should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if Morphine-EPD is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Morphine sulfate and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Morphine-EPD should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

Morphine-EPD may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of morphine sulfate with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, 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. Morphine sulfate should be used with extreme caution in patients with acute asthmatic attack, substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. The use of morphine in these patients should be reserved for those whose condition requires endotracheal intubation and respiratory support or control of ventilation (see **CONTRAINDICATIONS**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Morphine-EPD, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with Morphine-EPD and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of Morphine-EPD are essential. Overestimating the Morphine-EPD dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS**, Special Populations, **Special Risk Groups**, and **DOSAGE AND ADMINISTRATION**).

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Morphine-EPD, as in these patients, even usual therapeutic doses of Morphine-EPD may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Morphine-EPD is contraindicated in Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS**, **Post-Marketing Experience**).

Special Populations

Special Risk Groups: Morphine sulfate should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, in patients with the presence of increased intracranial/intraocular pressure (pupillary changes (miosis) may obscure the course of intracranial pathology), in patients with head injury, and in patients with decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis, chronic obstructive pulmonary disease, severely impaired pulmonary function), Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women: Studies in human have not been conducted. Morphine-EPD crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgement of the physician, potential benefits outweigh the risks.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS**, **Neonatal Opioid Withdrawal Syndrome (NOWS)**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, Morphine-EPD is not recommended to be used in nursing women and during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Morphine-EPD is used in this population.

Pediatrics (< 18 years of age): The safety and efficacy of Morphine-EPD have not been studied in the pediatric population. Therefore, use of Morphine-EPD is not recommended in patients under 18 years of age.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION**).

Patients with Hepatic or Renal Impairment:

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of Morphine-EPD (morphine sulfate injection) are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most serious side effect is respiratory depression. Bolus administration by the epidural route may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centers 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 AND OVERDOSAGE**). 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. Incidence is somewhat lower in females. Catheterization may be required (see **PRECAUTIONS**).

Type I Herpes Simplex has been observed in post-partum patients following epidural administration of morphine (see **PRECAUTIONS**).

Miscellaneous side effects include constipation, headache, anxiety, depression of cough reflex, interference with thermal regulation and oliguria. Evidence of histamine release such as urticaria, wheals and/or local tissue irritation may occur.

In general, side effects are amenable to reversal by narcotic antagonists. **NALOXONE HYDROCHLORIDE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR ADMINISTRATION IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS.**

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Post-Marketing Experience

Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile

dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). Morphine-EPD should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

Coadministration of morphine with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS**).

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

DOSAGE AND ADMINISTRATION

Morphine-EPD should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

For acute pain, it is recommended that Morphine-EPD be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 90 mg (90 morphine milligram equivalent) of Morphine-EPD not be exceeded. Each patient should be assessed for their risk prior to prescribing Morphine-EPD, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the

level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of Morphine-EPD (see **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**).

Dosing Considerations

Morphine-EPD (morphine sulfate injection) should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

Morphine-EPD is not indicated for rectal administration

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

Recommended Dose and Dosage Adjustment

Preservative-Free Morphine-EPD (morphine sulfate injection USP) should be administered epidurally only by physicians experienced in the techniques of epidural administration and who are thoroughly familiar with the labelling.

Refer to **Table 1** for the approximate equivalences for opioid analgesics.

Opioid Rotation

Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider reducing the calculated dose by 25-50% to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Table 1: OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES¹

Drug	Equivalent Dose (mg) ² (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine	10	60 ³	3-4
Oxycodone	15	30 ⁴	2-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine ⁶	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone ⁵	-	-	-
Heroin	5-8	10-15	3-4
Weak Opioid Agonists:			
Codeine	120	200	3-4
Propoxyphene	50	100	2-4

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Mixed Agonist-Antagonists⁷:

Pentazocine ⁶	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

Footnotes:

¹References:

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² Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25% to 50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.[†] Upward titration may be required to reach appropriate maintenance doses.

[†]Levy MH. Pharmacologic treatment of cancer pain. *N Engl J Med* 1996;335:1124-1132.

³ For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2-3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).

⁴ Based on single entity oral oxycodone in acute pain.

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

⁶ Not recommended for the management of chronic pain.

⁷ Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Epidural Administration

Proper placement of the needle or catheter in the epidural space, using appropriate sterile technique, should be verified before each injection of Preservative-Free Morphine Sulfate Injection. Acceptable techniques for verifying proper placement include: a) aspiration to check for absence of blood or cerebrospinal fluid, of b) administration of 5 mL (3 mL in obstetric patients) of unpreserved 1.5% Lidocaine and Epinephrine (1:200,000) injection, and then observe the patient for lack of tachycardia (this indicates that vascular injection has not been made), and lack of sudden onset of segmental anesthesia (this indicates that intrathecal injection has not been made).

Epidural Adult Dosage

It is recommended that the administration of Preservative-Free Morphine-EPD be limited to the lumbar area. Thoracic administration has been shown to increase the incidence of early and late respiratory depression, even at doses of 1 to 2 mg.

Initial bolus of 5 mg in the lumbar region usually provides satisfactory pain relief. Onset of analgesia generally occurs in 15-60 minutes and may last for up to 24 hours. If adequate pain relief is not achieved within one hour, careful administration of incremental doses of 1 to 2 mg at intervals sufficient to assess effectiveness may be given through an indwelling 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).

Patients of average build and weight: A single 5 mg dose of Preservative-Free Morphine-EPD 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 extreme caution. Doses of less than 5 mg may provide satisfactory pain relief for up to 24 hours.

Repeat Dosage

If pain recurs, Preservative-Free Morphine-EPD 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 narcotics. Cautious dosage and 24-hour observation for respiratory depression are mandatory under these conditions.

Epidural Pediatric Use

No information on the use of Preservative-Free Morphine-EPD in pediatric patients is available.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use the injection if its color is darker than pale yellow, or discolored in any other way, or if it contains a precipitate.

Geriatrics:

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. Morphine-EPD should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Use with Non-Opioid Medications:

If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. Morphine-EPD can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration:

Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage:

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Morphine-EPD. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, goosebumps, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Disposal

Morphine-EPD should be kept in a safe place, out of the sight and reach of children before, during and after use. Morphine-EPD should not be used in front of children, since they may copy these actions.

OVERDOSAGE

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

Symptoms:

Overdosage is characterized by respiratory depression with or without concomitant CNS depression.

Treatment:

Since respiratory arrest may result either through direct depression of the respiratory center or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone hydrochloride is a specific antidote. Naloxone (usually 0.4 mg) should be administered intravenously, 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. Note: Onset of respiratory depression may be delayed up to 24 hours following epidural administration. In painful conditions, reversal of narcotic 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. Parenteral

administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage. In the presence of physical dependence, naloxone may produce withdrawal symptoms.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 and miosis.

Pharmacodynamics

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 (i.e. an oil/water partition coefficient of 1.42) 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 prolonged effect. Morphine, as with other opiates, 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**).

Central Nervous System:

Morphine sulfate produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO₂ tension and to electrical stimulation.

Morphine sulfate depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine sulfate causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine sulfate overdose.

Gastrointestinal Tract and Other Smooth Muscle: Morphine sulfate causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System:

Morphine sulfate may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System: Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System: *In vitro* and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Pharmacokinetics

Peak serum levels following the epidural administration of preservative-free morphine sulfate injection are reached within 10 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 80 minutes following epidural administration; analgesia may last up to 24 hours.

Special Populations and Conditions

Pediatrics: Individuals under 18 years of age should not take Morphine-EPD.

STORAGE AND STABILITY

Store between 15°C and 30°C. Protect from light and freezing. DO NOT HEAT STERILIZE.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Morphine-EPD (morphine sulfate injection) is a sterile, non-pyrogenic isobaric solution of morphine sulfate in water for injection. The solution contains no antioxidant, bacteriostasis or antimicrobial agent.

Composition:

Each mL contains morphine sulfate 0.5 mg or 1 mg and sodium chloride 9 mg. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH is approximately 5.3 (2.5 to 6.5). Each ampoule is intended for single use only. Discard any unused portion.

Packaging:

Morphine-EPD (morphine sulfate injection) is supplied in ampoules as follows:

- 0.5 mg/mL in 10 mL (5 mg/10 mL)
- 1 mg/mL in 5 mL (5 mg/5 mL)

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:

Morphine sulfate pentahydrate

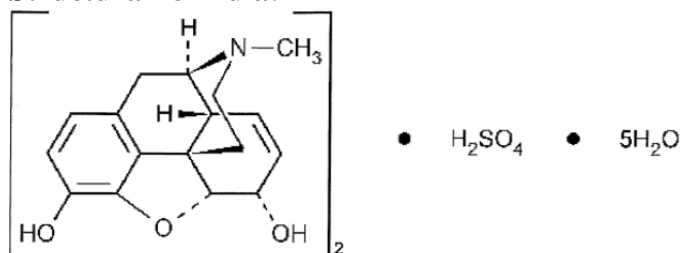
Chemical name:

7,8-Didehydro-4,5 α -epoxy-17-methylmorphinan-3,6 α -diol sulfate (2:1)(salt) pentahydrate

Molecular formula and molecular mass:

Molecular formula: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

Molecular mass: 758.83 g/mol

Structural formula:**Physicochemical Properties:**

A fine, white powder. When exposed to air it gradually loses water of hydration, and darkens on prolonged exposure to light. It is soluble in water and ethanol at room temperature.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**^NMorphine-EPD
(Morphine Sulfate Injection, USP)**

Read this carefully before you start taking Morphine-EPD. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Morphine-EPD.

Serious Warnings and Precautions

- **Even if you take Morphine-EPD as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking Morphine-EPD. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **If a person has not been prescribed Morphine-EPD, taking even one dose can cause a fatal overdose. This is especially true for children. If you took Morphine-EPD while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
 - **has changes in their breathing (such as weak, difficult or fast breathing)**
 - **is unusually difficult to comfort**
 - **has tremors (shakiness)**
 - **has increased stools, sneezing, yawning, vomiting, or fever****Seek immediate medical help for your baby.**
- **Taking Morphine-EPD with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is Morphine-EPD used for?

Morphine-EPD is an injection containing morphine sulfate (an opioid analgesic) used to control your pain.

How does Morphine-EPD work?

Morphine-EPD is a painkiller belonging to the class of drugs known as opioids. It relieves pain

by acting on specific nerve cells of the spinal cord and brain.

Morphine-EPD is used to treat severe pain in patients who need an opioid administered by epidural injection.

What are the ingredients in Morphine-EPD?

Medicinal ingredient: Morphine sulfate

Non-medicinal ingredient: Water for injection

Morphine-EPD comes in the following dosage form:

Solution for injection of 0.5 mg/mL and 1 mg/mL

Do not use Morphine-EPD if:

- your doctor did not prescribe it for you
- you are allergic to morphine sulfate or any of the other ingredients in Morphine-EPD
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Morphine-EPD. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines

- are planning to become pregnant

Other warnings you should know about:

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery: Opioids can be transferred to your baby through breast milk, or while still in the womb. Morphine-EPD can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using Morphine-EPD outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking Morphine-EPD, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking Morphine-EPD. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to Morphine-EPD. Morphine-EPD can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones.

You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off Morphine-EPD.

Serotonin Syndrome: Morphine-EPD can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take Morphine-EPD with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and

coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Morphine-EPD:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking Morphine-EPD. It can lead to:
 - drowsiness
 - unusually slow or weak breathing
 - serious side effects or
 - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by Morphine-EPD
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take Morphine-EPD with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take Morphine-EPD:

Morphine-EPD (morphine sulfate injection) should be administered epidurally only. **Patients with average build and weight:** Initial bolus of 5 mg in the lumbar region usually provides satisfactory pain relief. Onset of analgesia generally occurs in 15-60 minutes and may last 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. If pain recurs, Morphine-EPD 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. **Aged or debilitated patients:** Administer with extreme caution. Doses of less than 5 mg may provide satisfactory pain relief for up to 24 hours. **Pediatric Use:** No information on the use of Preservative-Free Morphine-EPD in pediatric patients is available.

Usual Adult Starting Dose:

Your dose is tailored/personalized just for you.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take Morphine-EPD for up to 7 days. If you need to take Morphine-EPD for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need Morphine-EPD. Be sure to use Morphine-EPD only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking Morphine-EPD, tell your doctor immediately.

Stopping your Medication

If you have been taking Morphine-EPD for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking Morphine-EPD. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking Morphine-EPD.

Refilling your Prescription for Morphine-EPD:

A new written prescription is required from your doctor each time you need more Morphine-

EPD.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

If you think you have taken too much Morphine-EPD, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

What are possible side effects from using Morphine-EPD?

These are not all the possible side effects you may feel when taking Morphine-EPD. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using Morphine-EPD.

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
RARE	Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			✓
	Respiratory Depression: slow, shallow or weak breathing.			✓
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
	Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
	Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
	Low Blood Pressure: dizziness, fainting, light-headedness.	✓		
	Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

3 ways to report:

- Online at MedEffect: <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>).

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.

Storage:

- **Keep unused or expired Morphine-EPD in a secure place to prevent theft, misuse or accidental exposure.**
- Store at controlled room temperature (15°C to 30°C). Protect from light and freezing.
- **Keep Morphine-EPD under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes Morphine-EPD, get emergency help right away.**

If you want more information about Morphine-EPD:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); or by calling 1-800-463-6001.

This leaflet was prepared by:

Hospira Healthcare Corporation,

Kirkland, Québec H9J 2M5

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