SUMMARY OF PRODUCT CHARATERISTICS

NAME OF THE MEDICINAL PRODUCT:

MORPHINE INJECTIONS 1 MG/ML

preservative-free
COMPOSITION:
Active ingredient: Morphine sulfate 1 mg/ml
Each ampoule of Morphine Injections 1 mg/ml contains morphine sulphate (5H2O) 1 mg/ml in a 5 ml ampoule.
Each ampoule also contains sodium chloride 9 mg/ml and water for injections.
Morphine Injections 1 mg/ml contains no preservatives.
Epidural, I.V, intrathecal

WARNING: SERIOUS AND LIFE THREATENING RISKS FROM USE OF MORPHINE INJECTIONS 1 MG/ML
Risks with Neuraxial Administration
Single-dose neuraxial administration may result in acute or delayed respiratory depression up to 24 hours. Because of the risk of severe adverse reactions when Morphine Injections 1 mg/ml is administered by the epidural or intrathecal route of administration, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose *[see Warnings and Precautions (5.1)]*.
Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Morphine Injections 1 mg/ml. Monitor for respiratory depression, especially during initiation of Morphine Injections 1 mg/ml or following a dose increase. Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid IV administration may result in overdosing *[see Warnings and Precautions (5.2)]*. To reduce the risk of respiratory depression, proper dosing and titration of Morphine Injections 1 mg/ml are essential.
Addiction, Abuse, and Misuse
Because the use of Morphine Injections 1 mg/ml exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Morphine Injections 1 mg/ml, and reassess all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.3)]*.
Neonatal Opioid Withdrawal Syndrome
Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated.
Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)]*.
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. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

1. INDICATIONS AND USAGE

Morphine Injections 1 mg/ml is indicated for:
The relief of pain that does not respond to treatment with non-opioid analgesics.
Morphine injection is a systemic opioid analgesic administered by the IV, epidural and intrathecal routes.
Morphine sulphate administered epidurally or intrathecally provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

2. DOSAGE AND ADMINISTRATION

General Dosing Information
Morphine sulphate preservative-free Injection is intended for IV, epidural or intrathecal administration.
Rapid IV 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 overdose reversal agent and equipment for artificial ventilation should be available.
Epidural or intrathecal administration of opioid analgesics should be performed only by physicians experienced in these techniques. Solutions containing a preservative must not be injected via these routes. Resuscitative equipment and medications, including a specific opioid overdose reversal agent (e.g., naloxone, nalmefene) should be immediately available for management of respiratory depression or other complications that may arise from inadvertent intrathecal or 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 *(see Warnings and Precautions)*.
For epidural or intrathecal administration, injection into the lumbar area may be preferred because of the increased risk of respiratory depression with injection into the thoracic area. Also, the epidural route is preferred, whenever possible, because of the increased risk of respiratory depression with intrathecal administration (*see Warnings and Precautions*).
Prior to epidural administration, proper placement of the needle or catheter in the epidural space must be verified. Aspiration to check for blood or cerebrospinal fluid may be performed; however, the fact that intravascular administration is possible even when aspiration for blood is negative must be kept in mind.
Alternatively, administration of 5 ml (3 ml for obstetrical patients) of preservative-free 1.5% lidocaine hydrochloride with epinephrine 1:200,000 injection may be used to verify placement in the epidural space. Tachycardia occurring after injection of the test medication indicates that the medication has entered the circulation; sudden onset of segmental anesthesia indicates that the medication has been administered intrathecally.
Following epidural or intrathecal injection of an opioid analgesic, administration of low doses of naloxone via continuous IV infusion for 24 hours may decrease the incidence of potential side effects without interfering with the analgesic effectiveness of the medication.
For the correct and effective use of morphine it is critical to adjust the dosing regimen for each patient individually according to the severity of pain, the patient's metabolism and condition, previous history of analgesic therapy, concurrent medications and response to morphine. The following dosage recommendations are, therefore, only suggested approaches to what is actually a series of clinical decisions in the management of pain of an individual patient.
IV Dosage
Adults
For IV administration, the initial dose is 4-10 mg of morphine sulphate/70 kg injected slowly over 4-5 minutes in adults.
Children
IV doses of 0.05-0.1 mg/kg body weight have been injected slowly in children.
In patients with exceptionally severe pain or in those who are tolerant to the analgesic effect of opiate agonists, it may be necessary to exceed the usual dosage. Patients vary greatly in their analgesic requirements and titration to achieve the desired therapeutic effect while minimizing side effects should be emphasized.
In the immediate postoperative period following surgical procedures associated with severe pain e.g. abdominal surgery, it is often preferable to administer opioids on a regular time schedule (round-the-clock) rather than on an as-needed basis after pain recurs. This avoids a delay between the recurrence of pain and onset of analgesia, causing needless suffering and adverse medical consequences for the patient. (For morphine, the dosing schedule is often every 4 hours.) It may be acceptable late in the postoperative course to switch to an as-needed schedule, as the patient's analgesic requirements diminish.
Epidural and Intrathecal Dosage
The usual initial epidural dose for injection in adults is 5 mg morphine sulphate preservative-free in the lumbar region, which may provide adequate pain relief for up to 24 hours. If adequate pain relief is not achieved within 1 hour after administration of the initial dose, additional epidural doses may be given carefully in 1 to 2 mg increments at intervals sufficient to assess efficacy, but generally no more than 10 mg total should be administered by epidural injection daily. Pain relief generally occurs within 15-60 minutes and persists for about 16-24 hours (range: 4-36 hours) after a single, effective epidural dose of morphine. For continuous epidural infusion when the device is not implanted surgically, an initial dosage of 2-4 mg per 24 hours has been recommended; epidural dosage may be increased by 1-2 mg daily if adequate relief is not achieved initially.
The intrathecal dosage of morphine sulphate is usually 1/10 that of the epidural dosage. A single 0.2 to 1 mg intrathecal dose may provide adequate relief for up to 24 hours in adults who are not tolerant to opiates. (Caution: this is only 0.2 to 1 ml of the 1 mg/ml potency. Do not inject intrathecally more than 1 ml of the 1 mg/ml potency.) Use in the lumbar area only is recommended.
Repeated intrathecal doses of the drug are not recommended except to establish initial intrathecal dosage when continuous intrathecal infusion is contemplated; if additional morphine therapy is necessary for patients who are not candidates for continuous intrathecal infusion, alternative routes of administration should be considered.
In debilitated or geriatric patients, epidural or intrathecal administration should be undertaken only with extreme caution, using relatively small doses.
Safety and efficacy of epidural or intrathecal administration in children have not been determined, and usage in this population is not recommended.
Important Dosage and Administration Instructions
Safety and Handling Instructions:
Morphine Injections 1 mg/ml is supplied in sealed ampoules. Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water.
Inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use, if the solution is discolored in any other way, or if it contains a precipitate.
Morphine Injections 1 mg/ml is intended for single use only. Protect from light, discard any unused portion. Do not heat-sterilize.
Initial Dosage
The starting dose of Morphine Injections 1 mg/ml must be individualized.
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5.3)]*.
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment experience and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.3)]*.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with Morphine Injections 1 mg/ml and adjust the dosage accordingly *[see Warnings and Precautions (5.2)]*.

Safe reduction and Discontinuation of Morphine Injections 1 mg/ml
When a patient who has been treated with a regimen of opioid analgesics including Morphine Injections 1 mg/ml regularly and may be physically dependent or no longer requires therapy with Morphine Injections 1 mg/ml, taper the dose gradually while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not rapidly reduce or abruptly discontinue Morphine Injections 1 mg/ml in a patients who may be physically dependent on opioids *[see Warnings and Precautions (5.16), Drug Abuse and Dependence (9.3)]*.

3. DOSAGE FORMS AND STRENGTHS

5 ml glass ampoules (5mg/5ml)

4. CONTRAINDICATIONS

Morphine Injections 1 mg/ml is contraindicated in patients with:
- Significant respiratory depression [*see Warnings and Precautions (5.2)*]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see Warnings and Precautions (5.9)*]
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days [*see Warnings and Precautions (5.10), Drug Interactions (7)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.14)]*
- Hypersensitivity to morphine (e.g., anaphylaxis) [*see Adverse Reactions (6)*]
- Hypersensitivity to any of the other ingredients in Morphine Injections.

Neuraxial administration of Morphine Injections 1 mg/ml is contraindicated in patients with *[see Warnings and Precautions (5.1)]*:
- Infection at the injection microinfusion site
- Concomitant anticoagulant therapy
- Uncontrolled bleeding diathesis
- The presence of any other concomitant therapy or medical condition which would render epidural or intrathecal administration of medication especially hazardous.

5. WARNINGS AND PRECAUTIONS

5.1 Risks with Neuraxial Administration

Control of pain by neuraxial opioid delivery is always accompanied by considerable risk to the patient and requires a high level of skill to be successfully accomplished. The task of treating these patients must be undertaken by experienced clinical teams, well-versed in patient selection, evolving technology and emerging standards of care.
In the case of epidural or intrathecal administration, Morphine Injections 1 mg/ml should be administered by or under the direction of a physician experienced in the techniques and familiar with the patient management problems associated with epidural or intrathecal drug administration. The physician should be familiar with patient conditions (such as infection at the injection site, bleeding diathesis, anticoagulant therapy, etc.) which call for special evaluation of the benefit versus risk potential.
Because epidural administration has been associated with less potential for immediate or late adverse effects than intrathecal administration, the epidural route should be used whenever possible.
For safety reasons, it is recommended that administration of Morphine Injections 1 mg/ml by the epidural or intrathecal routes be limited to the lumbar area. Thoracic epidural administration has been shown to dramatically increase the incidence of early and late respiratory depression even with doses of 1 to 2 mg.
Because of the risk of severe adverse effects when the epidural or intrathecal route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose.
The facility must be equipped to resuscitate patients with severe opiate overdosage, and the personnel must be familiar with the use and limitations of specific opioid overdose reversal agents (naloxone, naltrexone) in such cases.
Parenteral administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, 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 overdose reversal agents (e.g., naloxone, nalmefene), depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Morphine Injections 1 mg/ml, the risk is greatest during the initiation of therapy or following a dosage increase.
This respiratory depression and/or respiratory arrest may be severe and could require intervention.
- Because of delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing.
- Single-dose neuraxial administration may result in acute or delayed respiratory depression for periods at least as long as 24 hours.
- Severe respiratory depression up to 24 hours following epidural or intrathecal administration has been reported.
- Intrathecal use has been associated with a higher incidence of respiratory depression than epidural use.
- Thoracic administration has been shown to dramatically increase the incidence of early and late respiratory depression even at doses of 1 to 2 mg.

Because of the risk of severe adverse effects when the epidural or intrathecal route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose. The facility must be equipped to resuscitate patients with severe opiate overdosage, and the personnel must be familiar with the use and limitations of specific narcotic antagonists (naloxone, naltrexone) in such cases.
To reduce the risk of respiratory depression, proper dosing and titration of Morphine Injections 1 mg/ml are essential *[see Dosage and Administration (2)]*. Overestimating the Morphine Injections 1 mg/ml dosage can result in a fatal overdose with the first dose.
Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep- related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (Discontinuation of Morphine Injections 1 mg/ml)]*.

5.3 Addiction, Abuse, and Misuse

Morphine Injections 1 mg/ml contains morphine, a Schedule II controlled (FDA, USA) substance. As an opioid, Morphine Injections 1 mg/ml exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.
Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Morphine Injections 1 mg/ml. Addiction can occur at recommended dosages and if the drug is misused or abused. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use [see *Adverse Reactions (6)*].
Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Morphine Injections 1 mg/ml, and monitor all patients receiving Morphine Injections 1 mg/ml for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Morphine Injections 1 mg/ml, but use in such patients necessitates intensive counseling about the risks and proper use of Morphine Injections 1 mg/ml along with intensive monitoring for signs of addiction, abuse, and misuse.
Opioids are sought by drug users and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Morphine Injections 1 mg/ml. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of Morphine Injections 1 mg/ml during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that management by neonatology experts will be available at delivery *[see Use in Specific Populations (8.1)]*.

5.5 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from concomitant use of Morphine Injections 1 mg/ml with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
Use of neuroleptics in conjunction with neuraxial morphine may increase the risk of respiratory depression.
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 (7)]*.
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. Monitor 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 Injections 1 mg/ml 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 (7)]*.

5.6 Risk of Tolerance and Myoclonic Activity

Patients sometimes manifest unusual acceleration of neuraxial morphine requirements, which may cause concern regarding systemic absorption and the hazards of large doses; these patients may benefit from hospitalization and detoxification. Two cases of myoclonic-like spasm of the lower extremities have been reported in patients receiving more than 20 mg/day of intrathecal morphine. After detoxification, it might be possible to resume treatment at lower doses, and some patients have been successfully changed from continuous epidural morphine to continuous intrathecal morphine. Repeat detoxification may be indicated at a later date. The upper daily dosage limit for each patient during continuing treatment must be individualized.

5.7 Chest Wall Rigidity

Rapid intravenous administration may result in chest wall rigidity.

5.8 Opioid induced Hyperalgesia and Allodynia

Opioid Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect *[see Dependence (9.3)]*. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily nonpainful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.
Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) *[see Dosage and Administration (2), Warnings and Precautions (5.16)]*.

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of Morphine Injections 1 mg/ml in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.
Patients with Chronic Pulmonary Disease: Patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended doses of Morphine Injections 1 mg/ml *[see Warnings and Precautions (5.2)]*.
Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.
Monitor such patients closely, particularly when initiating and titrating Morphine Injections 1 mg/ml and when Morphine Injections 1 mg/ml is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2), Drug interactions (7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, including respiratory depression, coma, and confusion. Morphine Injections 1 mg/ml should not be used in patients taking MAOIs or within 14 days of stopping such treatment *[see Drug Interactions (7)]*.

5.11 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.

5.12 Severe Hypotension

Morphine Injections 1 mg/ml may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of Morphine Injections 1 mg/ml. In patients with circulatory shock, Morphine Injections 1 mg/ml may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Morphine Injections 1 mg/ml in patients with circulatory shock.

5.13 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Morphine Injections 1 mg/ml may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Morphine Injections 1 mg/ml. Morphine Injections 1 mg/ml should be used with extreme caution in patients with head injury or increased intracranial pressure. Pupillary changes (miosis) from morphine may obscure the existence, extent and course of intracranial pathology. High doses of neuraxial morphine may produce myoclonic events *[see Warnings and Precautions (5.6)]*. Clinicians should maintain a high index of suspicion for adverse drug reactions when evaluating altered mental status or movement abnormalities in patients receiving this modality of treatment.
Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Morphine Injections 1 mg/ml in patients with impaired consciousness or coma.

5.14 Risks of Gastrointestinal complications

Morphine Injections 1 mg/ml is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.
The morphine in Morphine Injections 1 mg/ml may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms. As significant morphine is released into the systemic circulation from neuraxial administration, the ensuing smooth muscle hypertonicity may result in biliary colic.
Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain) and, if necessary, adjust opioid therapy as clinically appropriate *[see Clinical Pharmacology (12.2)]*.

5.15 Risk of Seizures

Morphine Injections 1 mg/ml may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical setting associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Morphine Injections 1 mg/ml therapy.
Excitation of the central nervous system, resulting in convulsions, may accompany high doses of morphine given intravenously.

5.16 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including Morphine Injections 1 mg/ml. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *[see Drug Interactions (7)]*.
When discontinuing Morphine Injections 1 mg/ml, gradually taper the dosage *[see Dosage and Administration (Discontinuation of Morphine Injections 1 mg/ml)]*. Do not rapidly reduce or abruptly discontinue Morphine Injections 1 mg/ml *[see Drug Abuse and Dependence (9.3)]*.

5.17 Risks of Driving and Operating Machinery

Morphine Injections 1 mg/ml may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Morphine Injections 1 mg/ml and know how they will react to the medication.

5.18 Risks of Use in Patients with Urinary System Disorders

Urinary retention, which may persist 10 to 20 hours following single epidural or intrathecal administration, is frequently associated with neuraxial opioid administration and must be anticipated, more frequently in male patients than female patients. Urinary retention may also occur during the first several days of hospitalization for the initiation of continuous intrathecal or epidural morphine therapy. Early recognition of difficulty in urination and prompt intervention in cases of urinary retention is indicated. Patients who develop urinary retention have responded to cholinomimetic treatment and/or judicious use of catheters.

5.19 Risks of Use in Ambulatory Patients

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be monitored for the possible occurrence of orthostatic hypotension, a frequent complication in single-dose neuraxial morphine analgesia.

6. ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.5)]*
- Myoclonic Activity *[see Warnings and Precautions (5.6)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.8)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.11)]*
- Severe Hypotension *[see Warnings and Precautions (5.12)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.14)]*
- Seizures *[see Warnings and Precautions (5.15)]*
- Withdrawal *[see Warnings and Precautions (5.16)]*
- Urinary Retention *[see Warnings and Precautions (5.18)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.19)]*

The following adverse reactions associated with the use of morphine were identified in clinical studies or post marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most serious adverse reactions encountered during administration of Morphine Injections 1 mg/ml were respiratory depression and/or respiratory arrest.
Cardiovascular System: 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.
Central Nervous System: myoclonus, seizures, dysphoric reactions, toxic psychosis, dizziness, euphoria, anxiety, confusion, headache. Lumbar puncture-type headache is encountered in a significant minority of cases for several days following intrathecal catheter implantation and generally responds to bed rest and/or other conventional therapy.
Gastrointestinal System: Nausea, vomiting, constipation
Skin: Generalized pruritus, urticaria, wheals, and/or local tissue irritation. Single-dose epidural or intrathecal administration is accompanied by a high incidence of dose-related generalized pruritus.
Urinary System: Urinary retention, oliguria.
Peripheral edema: There are several reports of peripheral edema.
Other: Other adverse reactions reported following morphine therapy include depression of cough reflex, interference with thermal regulation.
Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Morphine Injections.
Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time *[see Clinical Pharmacology (12.2)]*.
Hyperalgesia and Allodynia:
Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see Warnings and Precautions (5.8)]*.
Hypoglycemia:
Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).
Opioid-induced esophageal dysfunction (OIED):
Cases of OIED have been reported in patients taking opioids and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term [see *Warnings and Precautions (5.14)]*.
Adverse Reactions from Observational Studies
A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either: 1) filled multiple extended-release/long-acting opioid analgesic prescriptions during a 90-day period (n=978); or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months.
Over 12 months:
- approximately 1% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to- severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and
- approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse *[defined in Drug Abuse and Dependence (9.2)]*, respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. *New long-term use* was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates. The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

7. DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with Morphine Injections 1 mg/ml.

Table 1 Clinically Significant Drug Interactions with Morphine Injections

Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death. The depressant effects of morphine are potentiated by the presence of other CNS depressants. Use of neuroleptics in conjunction with neuraxial morphine may increase the risk of respiratory depression *[see Warnings and Precautions (5.5)]*.
Intervention:	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. Monitor patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, psychotropic drugs, antihistamines, neuroleptics, gabapentinoids (gabapentin or pregabalin), other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.10)]*.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Morphine Injections if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.10)]*.
Intervention:	Do not use Morphine Injections in patients taking MAOIs or within 14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses of <u>other</u> opioids (such as oxycodone, hydromorphone, oxymorphone, hydrocodone, or buprenorphine) to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Examples:	phenelzine, tranylcypromine, linezolid.
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of Morphine Injections and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine.
Muscle Relaxants	
Clinical Impact:	Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Morphine Injections and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when Morphine Injections is used concomitantly with anticholinergic drugs.
Oral P2Y12 Inhibitors	
Clinical Impact:	The co-administration of oral P2Y12 inhibitors and intravenous morphine sulfate can decrease the absorption and peak concentration of oral P2Y12 inhibitors and delay the onset of the antiplatelet effect.
Intervention:	Consider the use of a parenteral antiplatelet agent in the setting of acute coronary syndrome requiring co-administration of intravenous morphine sulfate.
Examples:	clopidogrel, prasugrel, ticagrelor

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

<u>Risk Summary</u>

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*.

Available data with Morphine Injections in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. There are adverse outcomes reported with fetal exposure to opioid analgesics (see clinical considerations). Published studies with morphine use during pregnancy have not reported a clear association with morphine and major birth defects *[see Human Data]*.

In published animal reproduction studies, morphine administered subcutaneously during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) at 5 and 16 times the human daily dose of 60 mg based on body surface area (HDD) in hamsters and mice, respectively, lower fetal body weight and increased incidence of abortion at 0.4 times the HDD in the rabbit, growth retardation at 6 times the HDD in the rat, and axial skeletal fusion and cryptorchidism at 16 times the HDD in the mouse. Administration of morphine sulfate to pregnant rats during organogenesis and through lactation resulted in cyanosis, hypothermia, decreased brain weights, pup mortality, decreased pup body weights, and adverse effects on reproductive tissues at 3-4 times the HDD; and long-term neurochemical changes in the brain of offspring which correlate with altered behavioral responses that persist through adulthood at exposures comparable to and less than the HDD [*see Animal Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

<u>Clinical Considerations</u>

Fetal/Neonatal Adverse Reactions

Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agent, such as naloxone or nalmefene, must be available for reversal of opioid induced respiratory depression in the neonate. Morphine Injections is not recommended for use in women during and immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including Morphine Injections 1 mg/ml, can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

<u>Data</u>

Human Data

The results from a population-based prospective cohort, including 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any time during pregnancy, indicate no increased risk for congenital malformations. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design.

Animal Data

Formal reproductive and developmental toxicology studies for morphine have not been conducted. Exposure margins for the following published study reports are based on human daily dose of 60 mg morphine using a body surface area comparison (HDD).

Neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of morphine sulfate (35-322 mg/kg) on Gestation Day 8 to pregnant hamsters (4.7 to 43.5 times the HDD). A no adverse effect level was not defined in this study and the findings cannot be clearly attributed to maternal toxicity.

Neural tube defects (exencephaly), axial skeletal fusions, and cryptorchidism were reported following a single subcutaneous (SC) injection of morphine sulfate to pregnant mice (100-500 mg/kg) on Gestation Day 8 or 9 at 200 mg/kg or greater (16 times the HDD) and fetal resorption at 400 mg/kg or higher (32 times the HDD). No adverse effects were noted following 100 mg/kg morphine in this model (8 times the HDD). In one study, following continuous subcutaneous infusion of doses greater than or equal to 2.72 mg/kg to mice (0.2 times the HDD), exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted. The effects were reduced with increasing daily dose; possibly due to rapid induction of tolerance under these infusion conditions. The clinical significance of this report is not clear.

Decreased fetal weights were observed in pregnant rats treated with 20 mg/kg/day morphine sulfate (3.2 times the HDD) from Gestation Day 7 to 9. There was no evidence of malformations despite maternal toxicity (10% mortality). In a second rat study, decreased fetal weight and increased incidences of growth retardation were noted at 35 mg/kg/day (5.7 times the HDD) and there was a reduced number of fetuses at 70 mg/kg/day (11.4 times the HDD) when pregnant rats were treated with 10, 35, or 70 mg/kg/day morphine sulfate via continuous infusion from Gestation Day 5 to 20. There was no evidence of fetal malformations or maternal toxicity.

An increased incidence of abortion was noted in a study in which pregnant rabbits were treated with 2.5 (0.8 times the HDD) to 10 mg/kg morphine sulfate via subcutaneous injection from Gestation Day 6 to 10. In a second study, decreased fetal body weights were reported following treatment of pregnant rabbits with increasing doses of morphine (10-50 mg/kg/day) during the pre-mating period and 50 mg/kg/day (16 times the HDD) throughout the gestation period. No overt malformations were reported in either publication; although only limited endpoints were evaluated.

In published studies in rats, exposure to morphine during gestation and/or lactation periods is associated with: decreased pup viability at 12.5 mg/kg/day or greater (2 times the HDD); decreased pup body weights at 15 mg/kg/day or greater (2.4 times the HDD); decreased litter size, decreased absolute brain and cerebellar weights, cyanosis, and hypothermia at 20 mg/kg/day (3.2 times the HDD); alteration of behavioral responses (play, social-interaction) at 1 mg/kg/day or greater (0.2 times the HDD); alteration of maternal behaviors (e.g., decreased nursing and pup retrievals) in mice at 1 mg/kg or higher (0.08 times the HDD) and rats at 1.5 mg/kg/day or higher (0.2 times the HDD); and a host of behavioral abnormalities in the offspring of rats, including altered responsiveness to opioids at 4 mg/kg/day (0.7 times the HDD) or greater.

Fetal and/or postnatal exposure to morphine in mice and rats has been shown to result in morphological changes in fetal and neonatal brain and neuronal cell loss, alteration of a number of neurotransmitter and neuromodulator systems, including opioid and non-opioid systems, and impairment in various learning and memory tests that appear to persist into adulthood. These studies were conducted with morphine treatment usually in the range of 4 to 20 mg/kg/day (0.7 to 3.2 times the HDD).

Additionally, delayed sexual maturation and decreased sexual behaviors in female offspring at 20 mg/kg/day (3.2 times the HDD), and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed at 20 mg/kg/day (3.2 times the HDD). Decreased litter size and viability were observed in the offspring of male rats that were intraperitoneally administered morphine sulfate for 1 day prior to mating at 25 mg/kg/day (4.1 times the HDD) and mated to untreated females. Decreased viability and body weight and/or movement deficits in both first and second generation offspring were reported when male mice were treated for 5 days with escalating doses of 120 to 240 mg/kg/day morphine sulfate (9.7 to 19.5 times the HDD) or when female mice treated with escalating doses of 60 to 240 mg/kg/day (4.9 to 19.5 times the HDD) followed by a 5- day treatment-free recovery period prior to mating. Similar multigenerational findings were also seen in female rats pre-gestationally treated with escalating doses of 10 to 22 mg/kg/day morphine (1.6 to 3.6 times the HDD).

8.2 Lactation

<u>Risk Summary</u>

Morphine is present in breast milk. Published lactation studies report variable concentrations of morphine in breast milk with administration of immediate-release morphine to nursing mothers in the early postpartum period with a milk-to-plasma morphine AUC ratio of 2.5:1 measured in one lactation study. However, there is insufficient information to determine the effects of morphine on the breastfed infant and the effects of morphine on milk production. Lactation studies have not been conducted with Morphine Injections, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Morphine Injections 1 mg/ml and any potential adverse effects on the breastfed infant from Morphine Injections 1 mg/ml or from the underlying maternal condition.

<u>Clinical Considerations</u>

Monitor infants exposed to Morphine Injections 1 mg/ml through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of morphine is stopped, or when breastfeeding is stopped.

8.3 Females and Males of Reproductive Potential

<u>Infertility</u>

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

In published animal studies, morphine administration adversely effected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats *[see Nonclinical Toxicology (13)]*.

8.4 Pediatric Use

Adequate studies to establish the safety and effectiveness of spinal morphine in pediatric patients have not been performed, and usage in this population is not recommended.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to Morphine Injections 1 mg/ml. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were

co-administered with other agents that depress respiration. Titrate the dosage of Morphine Injections 1 mg/ml slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.9)]*.

The pharmacodynamic effects of neuraxial morphine in the elderly are more variable than in the younger population. Patients will vary widely in the effective initial dose, rate of development of tolerance and the frequency and magnitude of associated adverse effects as the dose is increased. Initial doses should be based on careful clinical observation following "test doses", after making due allowances for the effects of the patient's age and infirmity on his/her ability to clear the drug, particularly in patients receiving epidural morphine.

Morphine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic or Renal Impairment

The elimination half-life of morphine may be prolonged in patients with reduced metabolic rates and with hepatic and/or renal dysfunction. Hence, care should be exercised in administering Morphine Injections 1 mg/ml to patients with these conditions. High blood morphine levels, due to reduced clearance, may take several days to develop.

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Morphine Injections 1 mg/ml contains morphine, a Schedule II controlled (FDA, USA) drug substance.

9.2 Abuse

Morphine Injections 1 mg/ml contains morphine, a substance with a high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction [see Warnings and Precautions (5.3)].

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional non-therapeutic use of a prescription drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use, (e.g., continuing drug use despite harmful consequences, giving a higher priority given to drug use than to other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of Morphine Injections 1 mg/ml increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of Morphine Injections 1 mg/ml with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of Morphine Injections 1 mg/ml abuse include those with a history of prolonged use of any opioid, including products containing morphine, those with a history of drug or alcohol abuse, or those who use Morphine Injections 1 mg/ml in combination with other abused drugs.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Morphine Injections 1 mg/ml, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, is required.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

<u>Risks Specific to Abuse of Morphine Injections 1 mg/ml</u>

Abuse of Morphine Injections 1 mg/ml poses a risk of overdose and death. The risk is increased with concurrent use of Morphine Injections 1 mg/ml with alcohol and/or other CNS depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Morphine Injections 1 mg/ml should not be rapidly reduced or abruptly discontinued in a physically dependent patient *[see Dosage and Administration (Discontinuation of Morphine Injections 1 mg/ml)]*. If Morphine Injections 1 mg/ml is rapidly reduced or abruptly discontinued in a physically dependent patient, a withdrawal syndrome may occur, typically characterized by: restlessness, lacrimation, rhinorrhea, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10. OVERDOSAGE

<u>Clinical Presentation</u>

Acute overdose with Morphine Injections 1 mg/ml can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

<u>Treatment of Overdose</u>

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support measures.

For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene.

As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary. Patients should be closely observed for evidence of re-narcotization.

Because the duration of opioid reversal is expected to be less than the duration of action of morphine in Morphine Injections 1 mg/ml, particularly with epidural or intrathecal morphine, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid overdose reversal agent is suboptimal or only brief in nature, administer additional reversal agent as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the opioid overdose reversal agent will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the reversal agent administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the reversal agent should be initiated with care and by titration with smaller than usual doses of the reversal agent.

11. DESCRIPTION

Morphine Injections 1 mg/ml is a sterile, clear, colorless solution in 5 ml ampoules intended for intravenous, epidural, or intrathecal administration for single use only.

Each ml contains morphine sulfate 1 mg (5 mg/5ml) and sodium chloride 9 mg in water for injections. Contains no preservative or antioxidants.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Morphine is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of morphine is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with morphine.

Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

<u>Effects on the Central Nervous System</u>

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

Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Both early and late respiratory depression (up to 24 hours post dosing) have been reported following neuraxial administration. Circulation of the spinal fluid may also result in high concentrations of morphine reaching the brain stem directly.

<u>Effects on the Gastrointestinal Tract and Other Smooth Muscle</u>

Morphine 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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase, and opioid-induced esophageal dysfunction (OIED).

<u>Effects on the Cardiovascular System</u>

Morphine produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritis, flushing, red eyes, sweating, and/or orthostatic hypotension.

<u>Effects on the Endocrine System</u>

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Use of opioids for an extended period of time 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 *[see Adverse Reactions (6)]*.

<u>Effects on the Immune System</u>

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

<u>Concentration – Efficacy Relationships</u>

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with opioid agonists. The minimum effective analgesic concentration of morphine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance.

<u>Concentration – Adverse Reaction Relationships</u>

There is a relationship between increasing morphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

12.3 Pharmacokinetics

<u>Intravenous Administration</u>

Morphine has an apparent volume of distribution ranging from 1.0 to 4.7 L/kg after *intravenous dosage.* Protein binding is low, about 36%, and muscle tissue binding is reported as 54%. A blood-brain barrier exists, and when morphine is introduced outside of the CNS (e.g., *intravenously*), plasma concentrations of morphine remain higher than the corresponding CSF morphine levels. Conversely, when morphine is injected into the *intrathecal space*, it diffuses out into the systemic circulation slowly, accounting for the long duration of action of morphine administered by this route.

Morphine has a total plasma clearance which ranges from 0.9 to 1.2 L/kg/h (liters/kilogram/hour) in postoperative patients, but shows considerable interindividual variation. The major pathway of clearance is hepatic glucuronidation to morphine-3-glucuronide, which is pharmacologically inactive. The major excretion path of the conjugate is through the kidneys, with about 10% in the feces.

Morphine is also eliminated by the kidneys, 2 to 12% being excreted unchanged in the urine. Terminal half-life is commonly reported to vary from 1.5 to 4.5 hours, although the longer half-lives were obtained when morphine levels were monitored over protracted periods with very sensitive radioimmunoassay methods. The accepted elimination half-life in normal subjects is 1.5 to 2 hours.

<u>Epidural Administration</u>

Morphine, injected into the *epidural space*, is rapidly absorbed into the general circulation. Absorption is so rapid that the plasma concentration-time profiles closely resemble those obtained after intravenous or intramuscular administration. Peak plasma concentrations averaging 33–40 ng/ml (range 5–62 ng/ml) are achieved within 10 to 15 minutes after administration of 3 mg of morphine. Plasma concentrations decline in a multiexponential fashion. The terminal half-life is reported to range from 39 to 249 minutes (mean of 90 ± 34.3 min) and, though somewhat shorter, is similar in magnitude as values reported after intravenous and intramuscular administration (1.5–4.5 h). CSF concentrations of morphine, after epidural doses of 2 to 6 mg in postoperative patients, have been reported to be 50 to 250 times higher than corresponding plasma concentrations. The CSF levels of morphine exceed those in plasma after only 15 minutes and are detectable for as long as 20 hours after the injection of 2 mg of epidural morphine.

Approximately 4% of the dose injected epidurally reaches the CSF. This corresponds to the relative minimum effective epidural and intrathecal doses of 5 mg and 0.25 mg, respectively. The disposition of morphine in the CSF follows a biphasic pattern, with an early half-life of 1.5 h and a late phase half-life of about 6 h. Morphine crosses the dura slowly, with an absorption half-life across the dura averaging 22 minutes. Maximum CSF concentrations are seen 60–90 minutes after injection. Minimum effective CSF concentrations for postoperative analgesia average 150 ng/ml (range < 1-380 ng/ml).

<u>Intrathecal Administration</u>

The *intrathecal route* of administration circumvents meningeal diffusion barriers and, therefore, lower doses of morphine produce comparable analgesia to that induced by the epidural route. After intrathecal bolus injection of morphine, there is a rapid initial distribution phase lasting 15–30 minutes and a half- life in the CSF of 42–136 min (mean 90 ± 16 min). Derived from limited data, it appears that the disposition of morphine in the CSF, from 15 minutes post-intrathecal administration to the end of a six- hour observation period, represents a combination of the distribution and elimination phases. Morphine concentrations in the CSF averaged 332 ± 137 ng/ml at 6 hours, following a bolus dose of 0.3 mg of morphine. The apparent volume of distribution of morphine in the intrathecal space is about 22 ± 8 ml.

Time-to-peak plasma concentrations, however, are similar (5-10 min) after either epidural or intrathecal bolus administration of morphine. Maximum plasma morphine concentrations after 0.3 mg intrathecal morphine have been reported from < 1 to 7.8 ng/ml. The minimum analgesic morphine plasma concentration during Patient-Controlled Analgesia (PCA) has been reported as 20–40 ng/ml, suggesting that any analgesic contribution from systemic redistribution would be minimal after the first 30–60 minutes with epidural administration and virtually absent with intrathecal administration of morphine.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

<u>Carcinogenesis</u>

Long-term studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

<u>Mutagenesis</u>

No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the above positive findings, *in vitro* studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in Drosophila.

<u>Impairment of Fertility</u>

No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted.

Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies and higher incidence of pseudopregnancies at 20 mg/kg/day (3.2 times the HDD) were reported. Studies from the literature have also reported changes in hormonal levels in male rats (i.e., testosterone, luteinizing hormone) following treatment with morphine at 10 mg/kg/day or greater (1.6 times the HDD).

14. HOW SUPPLIED/STORAGE AND HANDLING

Morphine Injections 1 mg/ml is a preservative-free solution in clear ampoules, intended for single use administration.

Store below 25˚C protected from light. Keep stored in carton until time of use. Do not freeze. Morphine Injections 1 mg/ml contains no preservatives or antioxidant. Each ampoule of Morphine Injections 1 mg/ml is intended for single use only. Discard any unused portion. Do not heat-sterilize.

Morphine Injections 1 mg/ml is supplied in sealed ampoules. Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water.

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