SUMMARY OF PRODUCT CHARACTERISTICS

HIGHLY CONCENTRATED

1. NAME OF THE MEDICINAL PRODUCT

Morphine Injections 20 mg/ml (100mg/5 ml) (Preservative Free)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Each ml of morphine injection 20mg/ml contains 20 mg Morphine sulfate.

Excipients: each ampule also contains sodium chloride 7.43 mg/ml and water for injection.

3. PHARMACEUTICAL FORM

Solution for injection

Epidural, Intrathecal, Continuous Intravenous.

IMPORTANT! This leaflet refers to both neuraxial (epidural and intrathecal) administration and continuous IV administration. Text that refers only to neuraxial administration or only to continuous IV administration is delineated.

WARNING: SERIOUS AND LIFE-THRTENING RISKS FROM USE OF MORPHINE SULFATE INJECTION

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 20 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 (4.4)].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of MORPHINE INJECTIONS 20 MG/ML. Monitor for respiratory depression, especially during initiation of MORPHINE INJECTIONS 20 MG/ML or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of MORPHINE INJECTIONS 20 MG/ML are essential. ***[see Warnings and Precautions (4.4)].***

Addiction, Abuse, and Misuse

Because the use of MORPHINE INJECTIONS 20 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 20 MG/ML, and reassess regularly for the development of these behaviors and conditions ***[see Warnings and Precautions (4.4)].***

Neonatal Opioid Withdrawal Syndrome

If opioid use is required for an extended period of time in a pregnant woman, advise the patient 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 (4.4)].***

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 of MORPHINE INJECTIONS 20 MG/ML and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. ***[see Warnings and Precautions (4.4), Drug Interactions (4.6)]***

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

Morphine injection 20mg/ml (preservative-free) is a systemic opioid analgesic indicated only for IV, epidural and intrathecal infusion in the treatment of intractable chronic pain. It was developed for use in continuous microinfusion devices and the dosage requirements of the individual patient. Morphine injection 20mg/ml is primarily intended for patients who are opioid-tolerant. Morphine sulphate administered epidurally or intrathecally provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Morphine sulphate preservative-free injection is intended for IV, epidural or intrathecal administration.

Posology

General Dosing Information for Neuraxial (epidural, intathecal) Administration
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. Upon initiation of continuous intraspinal therapy and following any subsequent dosage increments that are substantial, patients should be monitored in an adequate setting for at least 24 hours. Such facilities should have available resuscitative equipment and medications, including oxygen and a specific antagonist (naloxone HCI injection), for the management of respiratory depression or other complications that may arise [*see Warnings and Precautions (4.4*)].

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 (4.4)].*
Prior to the initial 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 (3ml 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.

The desired amount of morphine should be withdrawn from the ampoule through a microfilter. To minimize risk from glass or other particles, the product must be filtered through a 5 micro (or smaller) microfilter before injecting into the microinfusion device. If dilution is required, 0.9% sodium chloride injection is recommended.

Dosage and administration

Specific Dosing Regimens

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, concomitant 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.

Dosage for Continuous IV Administration

For patients with severe chronic pain in whom the oral route is not feasible (e.g., bowel obstruction), parenteral opioids are needed. Since intermittent injections are expensive, uncomfortable, induce "clock watching" and are associated with the "bolus effect" (peak levels associated with intolerable adverse effects and trough levels associated with inadequate analgesia), a continuous IV infusion is preferable. Continuous IV infusions (CIVI) are especially suitable for patients who already require IV access and maintenance for other reasons. Opioid therapy with CIVI should usually be attempted prior to initiating intraspinal therapy since this route of administration is less invasive, less expensive and is associated with a lower risk of serious complications.

For patients transferring from oral opioids, standard equianalgesic tables should be consulted for calculating the total daily opioid dose in parenteral morphine equivalents. For CIVI, the daily parenteral morphine dose should be added to solution (e.g., 500ml saline) and delivered over the ensuing 24 hours (e.g., 20ml/ hour). A loading bolus of 15 mg may be given by slow IV injection at the start of the infusion. Arrangements for rescue medication for breakthrough pain should always be ensured. It is important to remember that all conversion tables/ratios are meant to serve only as a guide and the dosage must always be adjusted according to the patient's response. Following assessment, the initial dose should be titrated up or down accordingly, until analgesia is adequate and side effects minimal. Following initiation of the infusion and after any subsequent changes in the infusion rate that are substantial, the patient should be monitored closely for several hours in a setting where an opioid antagonist, oxygen and resuscitative equipment, and personnel trained in their use, are available.

During the course of treatment, the patient may experience a recurrence of pain due to an increase in the level of pain because of disease progression or the development of tolerance to the drug. If this occurs, an increase in the dosage may be required. As there is no upper limit to the amount of morphine that may be given in intractable oncologic pain, the quantity administered should be that which produces adequate analgesia with no or tolerable side effects.

In published reports of adults with severe, chronic pain, maintenance dosages of CIVI usually have ranged from 0.8-80mg/hr. In a limited number of children with severe, chronic cancer pain, maintenance dosages of 0.025-2.6mg/kg/hr have been infused IV (median 0.04-0.07).

Dosage for Neuraxial Administration

In most cases the patient who initiates therapy with continuous intraspinal opioids will have been treated previously (unsuccessfully) with opioids either orally or parenterally. A patient's intraspinal analgesic requirements can be estimated by using the following conversion ratio:

300 mg oral morphine equals

100 mg parenteral morphine equals

10 mg epidural morphine equals

1 mg intrathecal morphine

(For patients who previously took opioids other than morphine, standard equianalgesic tables should be consulted for calculating the total daily opioid dose in morphine equivalents.) It is important to remember that all conversion tables/ ratios are meant to serve only as a guide and the dosage must always be adjusted according to the patient's response. Patients whose pain is unusually severe or has a marked neuropathic component will often require higher intraspinal doses, while elderly patients will usually require lower

intraspinal doses.

In all cases, the starting dose must be individualized, based upon in-hospital evaluation of the response to serial single-dose epidural/intrathecal bolus injections of regular Morphine injections (preservative free) 0.5mg/ml and 1.0mg/ ml, with close observation of the analgesic efficacy and adverse effects prior to surgery involving the continuous microinfusion device.

The usual starting dose for continuous epidural infusion, based upon limited data in patients who have some degree of opioid tolerance, is 4.5 to 10mg/ day. (The recommended initial epidural dose in patients who are not tolerant to opioids ranges from 3.5 to 7.5mg/day. However, continuous intraspinal opioid administration in opioid-naive patients is not generally recommended!!) The dose requirements may increase significantly during treatment. The upper daily limit for each patient must be individualized. The published literature suggests that most patients with severe chronic intractable pain will eventually require 10-100 mg/day.

The recommended initial lumbar intrathecal dose range in patients with no tolerance to opioids is 0.2 to 1 mg/day. **However, continuous intraspinal opioid administration in opioid-naive patients is not generally recommended!!** The published range of doses for individuals who have some degree of opioid tolerance varies from 1 to 10mg/day. Limited experience with continuous intrathecal infusion of morphine has shown that the daily doses have to be increased over time. The upper daily dosage limit for each patient must be individualized. In a minority of patients, a daily dose of 10-20mg may be necessary. Doses greater than 20mg/day are rarely necessary and should be employed with caution since they may be associated with a higher likelihood of serious side effects such as myoclonus and respiratory depression.

During the course of treatment, the patient may experience a recurrence of pain due to an increase in the level of pain because of disease progression or the development of tolerance to the drug. If this occurs, an increase in the dosage may be required. As there is no upper limit to the amount of morphine that may be given in intractable oncologic pain, the quantity administered should be that which produces adequate analgesia with no or tolerable side effects.

If other measures to relieve pain (e.g. nerve blocks, cordotomy) are employed, the morphine dosage should be reduced to an appropriate level.

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 generally recommended [*see Use in Specific Populations (4.7)].*

4.3 CONTRAINDICATIONS

MORPHINE INJECTIONS 20 MG/ML is contraindicated in patients with:

- Significant respiratory depression [see Warnings and Precautions (4.4)]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see Warnings and Precautions (4.4)]
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days [see Warnings and Precautions (4.4); Drug Interactions (4.6)]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see Warnings and Precautions (4.4)]
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1(e.g., anaphylaxis) [see Adverse Reactions (4.5)]

Due to the high concentration of the 20 mg/ml injection, this formulation is contraindicated for use during labor. Due to the high concentration of the 20 mg/ml injection, this formulation is contraindicated for use in all pediatric patients who cannot reliably participate in the correct assessment of their own pain relief.

Neuraxial administration of MORPHINE INJECTIONS 20 MG/ML is also contraindicated in patients with:

- Infection at the injection microinfusion site [see Warnings and Precautions (4.4)]
- Concomitant anticoagulant therapy [see Warnings and Precautions (4.4)]
- Uncontrolled bleeding diathesis [see Warnings and Precautions (4.4)]
- The presence of any other concomitant therapy or medical condition which would render epidural or intrathecal administration of medication especially hazardous.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Risks with Neuraxial Administration

Control of pain by neuraxial opiate delivery, using a continuous microinfusion device, is always accompanied by considerable risk to the patients 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.

MORPHINE INJECTIONS 20 MG/ML should be administered by or under the direction of a physician experienced in the techniques of epidural or intrathecal administration 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 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 opioid overdosage, and the personnel must be familiar with the use and limitations of specific narcotic antagonists (naloxone, naltrexone) in such cases.

For safety reasons, it is recommended that administration of MORPHINE INJECTIONS 20 MG/ML by the intrathecal route be limited to the lumbar area.

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 opioid antagonists, depending on the patient's clinical status [see Overdosage (4.9)].
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 20 MG/ML, the risk is greatest during the initiation of therapy or following a dosage increase.

Continuous IV: Because of a delay in the maximum CNS effect with intravenously administered Morphine Injections 20 mg/ml (30 min), rapid administration may result in overdosing. Respiratory depression may be severe and could require intervention [see Overdosage (4.9)]. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of Morphine Injections 20 mg/ml.

Neuraxial: This respiratory depression and/or respiratory arrest may be severe and could require intervention.

- Because of the risk of severe adverse effects, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial (single) test dose and, as appropriate, for the first several days after catheter implantation. The facility must be equipped to resuscitate patients with severe opioid overdosage, and the personnel must be familiar with the use and limitations of specific narcotic antagonists (naloxone, naltrexone) in such cases.
- 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.
- Parenteral administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage.

To reduce the risk of respiratory depression, proper dosing and titration of MORPHINE INJECTIONS 20 MG/ML are essential *[see Method of Administration (4.2]*. Overestimating the MORPHINE INJECTIONS 20 MG/ML dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Neuraxial: improper or erroneous substitution of morphine injections 20 mg/ml for regular morphine injections (1 mg/ml) is likely to result in serious overdosage, leading to seizures, respiratory depression, and death.

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 Method of Administration (4.2)]*.

Addiction, Abuse, and Misuse

MORPHINE INJECTIONS 20 MG/ML contains morphine, a Schedule II controlled substance. As an opioid, MORPHINE INJECTIONS 20 MG/ML exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (4.8)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed MORPHINE INJECTIONS 20 MG/ML. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing MORPHINE INJECTIONS 20 MG/ML, and monitor all patients receiving MORPHINE

INJECTIONS 20 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 20 MG/ML, but use in such patients necessitates intensive counseling about the risks and proper use of MORPHINE INJECTIONS 20 MG/ML along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing MORPHINE INJECTIONS 20 MG/ML. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Each ampul of MORPHINE INJECTIONS 20 MG/ML contains a large amount of a potent narcotic which has been associated with abuse and dependence among health care providers. Due to the limited indications for this product, the risk of overdosage and the risk of its diversion and abuse, it is recommended that special measures must be taken to control this product within the hospital or clinic. MORPHINE INJECTIONS 20 MG/ML should be subject to rigid accounting, rigorous control of wastage, and restricted access.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of MORPHINE INJECTIONS 20 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 appropriate treatment will be available at delivery *[see Use in Specific Populations 4.7]*.

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 20 MG/ML with benzodiazepines or other CNS depressants, (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Neuraxial: 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 (4.6)]*.

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 INJECTIONS 20 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 (4.6)]*.

Risk of Inflammatory Masses (Neuraxial)

Inflammatory masses such as granulomas, some of which have resulted in serious neurologic impairment including paralysis, have been reported to occur in patients receiving continuous infusion of opioid analgesics including MORPHINE INJECTIONS 20 MG/ML via indwelling intrathecal catheter. Patients receiving continuous infusion of MORPHINE INJECTIONS 20 MG/ML via indwelling intrathecal catheter should be carefully monitored for new neurologic signs or symptoms. Further assessment or intervention should be based on the clinical condition of the individual patient.

Risk of Tolerance and Myoclonic Activity (Neuraxial)

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.

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. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. 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 non-painful 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 (4.2), Warnings and Precautions (4.4)]*.

Cardiovascular Instability

Continuous IV: While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulatory catecholamines. Have naloxone injection and resuscitative equipment immediately available for use in case of life-threatening or intolerable side effects and whenever morphine therapy is being initiated.

Neuraxial: See Adverse Reactions for text on cardiovascular instability with neuraxial administration.

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

The use of MORPHINE INJECTIONS 20 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 20 MG/ML *[see Warnings and Precautions (4.4)]*.

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 (4.4)]*.

Monitor such patients closely, particularly when initiating and titrating MORPHINE INJECTIONS 20 MG/ML and when MORPHINE INJECTIONS 20 MG/ML is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (4.4)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, including respiratory depression, coma, and confusion. Morphine Injections 20 mg/ml should not be used in patients taking MAOIs or within 14 days of stopping such treatment *[see Drug Interactions (4.6)]*.

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.

Severe Hypotension

MORPHINE INJECTIONS 20 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 (4.6)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of MORPHINE INJECTIONS 20 MG/ML. In patients with circulatory shock, MORPHINE INJECTIONS 20 MG/ML may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of MORPHINE INJECTIONS 20 MG/ML in patients with circulatory shock.

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 20 MG/ML may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for worsening signs of increasing intracranial pressure. Monitor patients for signs of sedation and respiratory depression, particularly when initiating therapy with MORPHINE INJECTIONS 20 MG/ML.

Neuraxial: MORPHINE INJECTIONS 20 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 (4.4)]*. 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 20 MG/ML in patients with impaired consciousness or coma.

Risks of Use in Patients with Gastrointestinal Conditions

MORPHINE INJECTIONS 20 MG/ML is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The morphine in MORPHINE INJECTIONS 20 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.

Neuraxial: As significant morphine is released into the systemic circulation from neuraxial administration, the ensuing smooth muscle hypertonicity may result in biliary colic.

Increased Risk of Seizures in Patients with Seizure Disorders

The morphine in MORPHINE INJECTIONS 20 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 20 MG/ML therapy.

Continuous IV: Excitation of the central nervous system, resulting in convulsions, may accompany high doses of morphine given intravenously.

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 20 MG/ML. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing MORPHINE INJECTIONS 20 MG/ML in a physically-dependent patient, gradually taper the dosage *[see Dosage and Administration (4.2)]*. Do not abruptly discontinue MORPHINE INJECTIONS 20 MG/ML in these patients *[see Drug Abuse and Dependence (4.8)]*.

Risks of Driving and Operating Machinery

MORPHINE INJECTIONS 20 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 20 MG/ML and know how they will react to the medication.

Risks of Use in Patients with Urinary System Disorders (Neuraxial)

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.

Risks of Use in Ambulatory Patients (Neuraxial)

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.

4.5 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections *[see Warnings and Precautions (4.4)*]:

- Life-Threatening Respiratory Depression
- Addiction, Abuse, and Misuse
- Neonatal Opioid Withdrawal Syndrome
- Interactions with Benzodiazepines or Other CNS Depressants
- Neuraxial: Inflammatory Masses
- Neuraxial: Myoclonic Activity
- Continuous IV: Cardiovascular Instability
- Opioids-induced Hyperalgesia and allodynia
- Adrenal Insufficiency
- Severe Hypotension
- Gastrointestinal Adverse Reactions
- Seizures
- Withdrawal
- Neuraxial: Urinary Retention
- Neuraxial: Orthostatic Hypotension

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.

Adverse Reactions Associated with Neuraxial Administration:

The most serious adverse reactions encountered during continuous intrathecal or epidural infusion of MORPHINE INJECTIONS 20 MG/ML were respiratory depression, myoclonus, and formation of inflammatory masses.

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. Excitation of the central nervous system, resulting in convulsions, may accompany high doses of morphine given intravenously.

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: Pruritus, urticaria, wheals, and/or local tissue irritation

Genito-Urinary System: Urinary retention, oliguria, unexplained genital swelling in male patients, following infusion-device implant surgery.

Other: Other adverse experiences reported following morphine therapy include depression of cough reflex, interference with thermal regulation, peripheral edema.

Adverse Reactions Associated with Continuous IV Administration:
Serious adverse reactions associated with Morphine Injections 20 mg/ml include respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest. Rarely,

anaphylactoid reactions have been reported when morphine or other phenanthrene alkaloids of opium are administered intravenously.

The most frequently observed adverse reactions included sedation, lightheadedness, dizziness, nausea, vomiting, constipation, and diaphoresis.

Other possible adverse reactions included:

Central Nervous System – Euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, visual disturbances, transient hallucinations and disorientation.

Gastrointestinal – Constipation, biliary tract spasm.

Cardiovascular – Tachycardia, bradycardia, palpitation, faintness, syncope, and orthostatic hypotension.

Genitourinary – Oliguria and urinary retention; an antidiuretic effect has been reported.

Allergic – Pruritus, urticaria, and skin rashes. Anaphylactoid reactions have been reported following intravenous administration.

Other – Opioid-induced histamine release may be responsible for the flushing of the face, diaphoresis, and pruritus often seen with these drugs. Wheals and urticaria at the site of injection are probably related to histamine release. Local tissue irritation, pain and induration have been reported following repeated subcutaneous injection. Morphine may alter temperature regulation in susceptible individuals and will depress the cough reflex.

Adverse Reactions Associated with Both Neuraxial and Continuous IV Administration:

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 20 MG/ML.

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for extended period of time *[see Pharmaceutical Properties (5)].*

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *(see Warnings and Precautions (4.4)).*

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were on patients with at least one predisposing risk factor (e.g., diabetes).

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/

4.6 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with MORPHINE INJECTIONS 20 MG/ML.

Table 1. Clinically Significant Drug Interactions with MORPHINE INJECTIONS 20 MG/ML

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. Neuraxial: 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.
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.
Examples:	Alcohol, benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, psychotropic drugs, antihistamines, neuroleptics, other opioids**.**
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue MORPHINE INJECTIONS 20 MG/ML 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 (4.4)]*.
Intervention:	Do not use MORPHINE INJECTIONS 20 MG/ML 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 20 MG/ML 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 20 MG/ML 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 20 MG/ML is used concomitantly with anticholinergic drugs.
Oral $P2Y_{12}$ Inhibitors	
Clinical Impact:	The co-administration of oral $P2Y_{12}$ inhibitors and intravenous morphine sulfate can decrease the absorption and peak concentration of oral $P2Y_{12}$ inhibitors and delay the onset of the antiplatelet effect.
Intervention	Consider the use of parenteral antiplatelet agent in the setting of acute coronary syndrome requiring co-administration of intravenous morphine sulfate.
Examples	clopidogrel, prasugrel, ticagrelor
Cimetidine – Continuous IV only	
Clinical impact	Concomitant administration of Morphine sulfate injection and cimetidine has been reported to precipitate apnea, confusion, and muscle twitching in an isolated report.
Intervention	Monitor patients for increased respiratory and CNS depression when receiving cimetidine concomitantly with Morphine Sulfate Injection.

4.7 USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy can cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (4.4)].* There are no available data with MORPHINE INJECTIONS 20 MG/ML in pregnant women to inform a drug-associated risk for major birth defects and miscarriage or adverse maternal outcomes. 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 (in4.7)].* 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 in (4.7)*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The 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.

Clinical Considerations

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 (4.4)].*

Labor or Delivery

Opioids, including intravenously, epidurally, and intrathecally administered morphine, readily cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, and resuscitative equipment must be

available for reversal of opioid-induced respiratory depression in the neonate. MORPHINE INJECTIONS 20 MG/ML is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate (*see Contraindications* 4.3). Opioid analgesics, including MORPHINE INJECTIONS 20 MG/ML, can prolong labor through actions which 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 dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Neuraxial: MORPHINE INJECTIONS 20 MG/ML is too highly concentrated for routine use in obstetric neuraxial analgesia (*see Contraindications 4.3*).

Data

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).

Lactation

Risk Summary

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 20 MG/ML, 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 20 MG/ML and any potential adverse effects on the breastfed infant from MORPHINE INJECTIONS 20 MG/ML or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to MORPHINE INJECTIONS 20 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.

Females and Males of Reproductive Potential

Infertility

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 (4.5), Pharmaceutical properties (5)]*.

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 (5.3)]*.

Pediatric Use

The safety and effectiveness of MORPHINE INJECTIONS 20 MG/ML in pediatric patients below the age of 18 have not been established, and usage in this population is **not** recommended.

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to MORPHINE INJECTIONS 20 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 20 MG/ML slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (4.4)]*.

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.

Neuraxial: 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.

Hepatic or Renal Impairment

Neuraxial: 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 20 MG/ML epidurally to patients with these conditions. High blood morphine levels, due to reduced clearance, may take several days to develop.

Continuous IV: Morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Start these patients with a lower than normal dosage of Morphine Injections 20 mg/ml and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension *[see Pharmaceutical properties (5)].* Morphine pharmacokinetics are altered in patients with renal failure. Start these patients with a lower than normal dosage of Morphine Injections 20 mg/ml and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension *[see Pharmaceutical properties (5)*

4.8 DRUG ABUSE AND DEPENDENCE

Controlled Substance

MORPHINE INJECTIONS 20 MG/ML contains morphine, a Schedule II controlled drug substance.

Abuse

MORPHINE INJECTIONS 20 MG/ML contains morphine, a substance with a high potential for abuse and misuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (4.4)]*.
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 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 to drug use that to other activities and obligations),and possible tolerance or physical dependence.

Misuse and abuse of Morphine Sulfate Injection 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 Sulfate Injection 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 Sulfate Injection 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 Sulfate Injection 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.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

MORPHINE INJECTIONS 20 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, as required by state and federal law, is strongly advised.

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.

Risks Specific to Abuse of Morphine Injection 20mg/ml

Abuse of Morphine Injection poses a risk of overdose and death. The risk is increased with concurrent use of Morphine Sulfate Injection with alcohol and/or other CNS depressants.

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

Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is a physiological state characterized by a reduced response to drug 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), 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 20 MG/ML should not be abruptly discontinued *[see Dosage and Administration (4.2)]*. If MORPHINE INJECTIONS 20 MG/ML is 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 (4.7)].

4.9 OVERDOSAGE

Clinical Presentation

Acute overdose with MORPHINE INJECTIONS 20 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 Pharmaceutical properties (5)]*.

Treatment of Overdose

In case of overdose, priorities are the reestablishment 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.

Opioid antagonists, such as naloxone , are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer an opioid antagonist.

Neuraxial: 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 renarcotization.

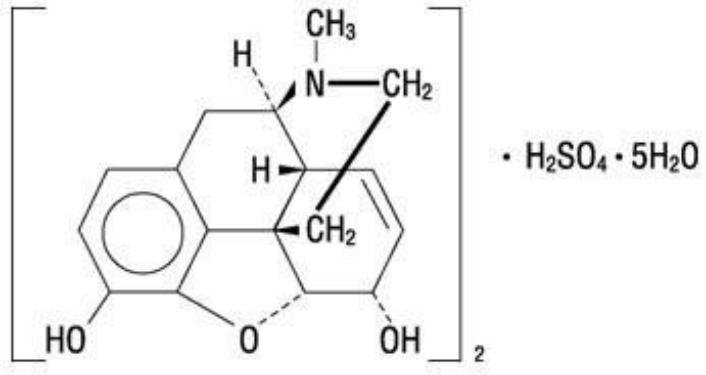
Because the duration of opioid reversal is expected to be less than the duration of action of morphine in MORPHINE INJECTIONS 20 MG/ML, particularly with epidural or intrathecal morphine, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist 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 antagonist administered. If a decision is made to treat serious respiratory depression in the physically-dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

5 PHARMACOLOGICAL PROPERTIES

Description

Morphine is an opioid agonist. Morphine is the most important alkaloid of opium and is a phenanthrene derivative. It is available as the sulfate salt, chemically identified as 7,8-Didehydro-4,5-epoxy-17- methyl-(5α,6α)-morphinan-3,6-diol sulfate (2:1) (salt), pentahydrate, with the following structural formula:



$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ Molecular Weight is 758.83

Morphine sulfate USP is an odorless, white crystalline powder with a bitter taste. When exposed to air, it gradually loses hydration, and darken on prolonged exposure to light. It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol: water partition coefficient of morphine is 1.42 at physiologic pH and the pKa is 7.9 for the tertiary nitrogen (the majority is ionized at pH 7.4).

Morphine Injections 20 mg/ml (preservative-free morphine sulfate sterile solution) is available as a sterile, high potency solution of morphine sulfate in a strength of 20 mg morphine sulfate per mL, free of antioxidants, preservatives or other potentially neurotoxic additives.

Morphine Injections 20 mg/ml is intended for use in continuous microinfusion devices for intravenous and intraspinal administration in the management of pain.

Each mL of Morphine Injections 20 mg/ml contains morphine sulfate and sodium chloride 7.43 mg in Water for Injection. Contains no preservative. Each ampoule of Morphine Injections 20 mg/ml is intended for **SINGLE USE ONLY**.

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.

5.1 PHARMACODYNAMICS

Effects on the Central Nervous System

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.

Neuraxial: 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.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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.

Effects on the Cardiovascular System

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 and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and lutenizing hormone (LH) in humans *[see Adverse Reactions (4.5)]*. 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 (4.5)]*.

Effects on the Immune System

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.

Concentration – Efficacy Relationships

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 *[see Dosage and Administration (4.2)]*.

Concentration – Adverse Reaction Relationships

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 *[see Dosage and Administration (4.2)]*.

5.2 Pharmacokinetics

Epidural Administration

Absorption

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.

Distribution

Plasma concentrations decline in a multiexponential fashion. 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).

Elimination

The terminal half-life is reported to range from 39 to 249 minutes (mean of 90 ± 34.3 min) for epidural administration.

Metabolism

The major pathway of clearance is hepatic glucuronidation to morphine-3-glucuronide, which is pharmacologically inactive.

Excretion

The major excretion path of the morphine-3-glucuronide 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.

Intrathecal Administration

Absorption

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.

Distribution

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.

Intravenous administration

Distribution

Morphine has an apparent volume of distribution ranging from 1.0 to 4.7 L/kg after parenteral administration. 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, plasma concentrations of morphine remain higher than the corresponding CSF morphine levels.

Elimination

Morphine has a total plasma clearance which ranges from 0.9 to 1.2 L/kg/h in postoperative patients, but shows considerable inter individual variation.

Metabolism

The major pathway of clearance is hepatic glucuronidation to morphine-3-glucuronide, which is pharmacologically inactive.

Excretion

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.

Specific population

Gender

While evidence of greater post-operative Morphine Injections 20 mg/ml consumption in men compared to women is present in the literature, clinically significant differences in analgesic outcomes and pharmacokinetic parameters have not been consistently demonstrated. Some studies have shown an increased sensitivity to the adverse effects of Morphine Injections 20 mg/ml, including respiratory depression, in women compared to men.

Hepatic Impairment

Morphine pharmacokinetics are altered in patients with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine AUC ratios also decreased in these subjects, indicating diminished metabolic activity. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted.

Renal Impairment

Morphine pharmacokinetics are altered in patients with renal failure. The AUC is increased and clearance is decreased and the metabolites, M3G and M6G, may accumulate to much higher plasma

levels in patients with renal failure as compared to patients with normal renal function. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.

5.3 NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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.

Impairment of Fertility

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).

Female rats that were administered morphine sulfate intraperitoneally prior to mating exhibited prolonged estrous cycles at 10 mg/kg/day (1.6 times the HDD).

Exposure of adolescent male rats to morphine has been associated with delayed sexual maturation 6.1and following mating to untreated females, smaller litters, increased pup mortality, and/or changes in reproductive endocrine status in adult male offspring have been reported (estimated 5 times the plasma levels at the HDD).

6.PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each ampoule also contains sodium chloride 7.43 mg/ml and water for injection.
Morphine Injections 20 mg/ml contains no preservatives.

Morphine Injections 20mg/ml is a clear and colorless to pale yellow preservative-free solution supplied as a sterile solution in sealed clear glass ampoules.

Not for single dose epidural, intrathecal or IV administration, but rather only as continuous infusion.

Neuraxial administration: Morphine Injections 20 mg/ml are for epidural and intrathecal infusion using a continuous microinfusion device, and only after filtering through a microfilter (5 microns or smaller). If dilution is required use 0.9% Sodium Chloride injection.
Continuous IV administration: Morphine Injections 20 mg/ml are for continuous IV infusion only after dilution in either Dextrose 5% injection or Sodium Chloride 0.9% injection to a final concentration of 0.1 mg/ml to 5 mg/ml, as determined by the patient's needs, prior administration.

6.2 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25˚C, protected from light. Keep stored in carton until time of use.
Morphine Injections 20 mg/ml contains no preservatives or antioxidants.

Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the injection is darker than pale yellow or if it contains a precipitate.

6.3 INCOMPATIBILITIES

Morphine sulphate has been reported to be physically or chemically incompatible with solutions containing aminophylline, amobarbital sodium, chlorothiazide sodium, heparin sodium, meperidine hydrochloride, methicillin sodium, nitrofurantoin sodium, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, sodium bicarbonate, sodium iodide, thiopental sodium, sulfadiazine and sulfisoxazole.

Each 5 ml ampoule of Morphine Injections 20mg/ml contains 100 mg morphine sulphate and therefore it is recommended that special measures be taken to control this product within the hospital or clinic. Consideration should be given to the limited indications for this product, the risk of overdosage and risk of its diversion and abuse.

Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water.

6.4 SHELF LIFE

The expiry date of the product is indicated on the packaging materials.
Each ampoule of Morphine Injections 20 mg/ml is intended for single use only. Discard any unused portion.

6.5 NATURE AND CONTENT OF CONTAINER

Clear colourless to yellowish solution in translucent 5 ml ampoules.

7. REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O. Box 405, Jerusalem 9100301, Israel.
Registration number: 106-25-28981

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