Parameters	Remarks		Parameters	Remarks
Product name/Generic name	Mitigo (morphine sulfate inj., USP)		Market/Country	USA
Strength	N/A		Barcode	N/A
Component	Insert leaflet		Material Code	028015
Dimensions	482.6 x 454.03 mm		Superseded Material Code	024973
Specification	N/A		Artwork Number	N/A
Font Set & Min. Size	Arial Narrow 8pt.		Superseded Artwork Number	N/A
Pantone number	Process Black	DieLine - no print	MAH	PCC Inc. USA
Cut Margins/Peel off Margins	N/A		GTIN	N/A
Unvarnished Zone	N/A		Special Instructions	N/A
			Pharma Code	N/A
Reason for revision:				
Date: 24 May 2021	Created by: JZ	**Proof#**: 2	Filename: 028015_Mitigo_USA_Pi_INS_04_21.indd	

482.6 mm

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454.03 mm 304.01 mm 78.58 mm

MITIGO
(morphine sulfate injection, USP – Preservative-free) injectable solution
028015

MITIGO
(morphine sulfate injection, USP – Preservative-free) injectable solution
028015

304.01 mm 78.58 mm

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MITIGO safely and effectively. See full prescribing information for MITIGO.

MITIGO (morphine sulfate injection, USP - Preservative-free) injectable solution for intrathecal or epidural infusion, using a continuous microinfusion device, CII

Initial U.S. Approval: 1941

WARNING: RISKS WITH NEURAXIAL ADMINISTRATION; LIFE-THREATENING RESPIRATORY DEPRESSION; RISK OF ADDICTION, ABUSE, AND MISUSE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **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 MITIGO 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)].**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Patients must be observed in a fully equipped and staffed environment for at least 24 hours after each test dose and, as indicated, for the first several days after surgery. (5.2)**
- **MITIGO exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.3)**
- **Prolonged use of MITIGO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **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; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5, 7)**

---INDICATIONS AND USAGE---

MITIGO (Morphine Sulfate Injection, USP – Preservative-free) is an opioid agonist, for use in continuous microinfusion devices and indicated only for intrathecal or epidural infusion in the management of intractable chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

---DOSAGE AND ADMINISTRATION---

- Administration should be limited to use by those familiar with the management of respiratory depression. (2.1)
- Should be administered by or under the direction of a physician experienced in the techniques of epidural or intrathecal administration. (2.1)
- Patients should be observed in a fully equipped and staffed environment for at least 24 hours after each test dose and, as indicated, for the first several days after surgery. (2.1)
- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. (2.2) Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.2)
- Initial Dosage: Must be individualized, based upon in-hospital evaluation of the response to serial single-dose epidural bolus injections of regular morphine sulfate injection, USP 0.5 mg/mL or 1 mg/mL, with close observation for analgesic efficacy and adverse effects prior to surgery involving the continuous microinfusion device. (2.2)
- Dosage for Epidural Administration: Initial dose range of 3.5 to 7.5 mg/day for patients with no tolerance to opioids. The usual starting dose for continuous epidural infusion in patients with some degree of opioid tolerance is 4.5 to 10 mg/day and may increase significantly during treatment to 20-30 mg/day. (2.3)
- Dosage for Intrathecal Administration: Initial dose range of 0.2 to 1 mg/day for patients with no tolerance to opioids. The range of doses for patients with some degree of opioid tolerance varies from 1 to 10 mg/day. Doses above 20 mg/day should be employed with caution. (2.4)
- Do not stop MITIGO abruptly in a physically dependent patient. (2.6)

---DOSAGE FORMS AND STRENGTHS---

Injection: 200 mg/20 mL (10 mg/mL) Preservative-free amber glass single-dose vials

Injection: 500 mg/20 mL (25 mg/mL) Preservative-free amber glass single-dose vials (3)

---CONTRAINDICATIONS---

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting in absence of resuscitative equipment (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity or intolerance to morphine (4)

Neuraxial administration of MITIGO is contraindicated in patients with:

- Infection at the injection microinfusion site (4)
- Concomitant anticoagulant therapy (4)
- Uncontrolled bleeding diathesis (4)
- The presence of any other concomitant therapy or medical condition which would render epidural or intrathecal administration of medication especially hazardous. (4)

---WARNINGS AND PRECAUTIONS---

- Risk of Inflammatory Masses: Monitor patients receiving continuous infusion of MITIGO via indwelling intrathecal catheter for new signs or symptoms of neurologic impairment. (5.6)
- Risk of Tolerance and Myoclonic Activity: Monitor patients for unusual acceleration of neuraxial morphine, which may cause myoclonic-like spasm of lower extremities. Detoxification may be required. (5.7)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of MITIGO in patients with circulatory shock. (5.11)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of MITIGO in patients with impaired consciousness or coma. (5.12)

---ADVERSE REACTIONS---

Most serious adverse reactions were respiratory depression, apnea, circulatory depression, respiratory arrest, shock, and cardiac arrest. Other common frequently observed adverse reactions include: sedation, lightheadedness, dizziness, nausea, vomiting, and constipation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Piramal Critical Care, Inc. at 1-888-822-8431 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---DRUG INTERACTIONS---

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue MITIGO if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with MITIGO because they may reduce the analgesic effect of MITIGO or precipitate withdrawal symptoms. (7)

---USE IN SPECIFIC POPULATIONS---

- Pregnancy: May cause fetal harm. (8.1)
- Hepatic and Renal Impairment: May affect the metabolism and excretion of MITIGO. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

BOXED WARNING

WARNING: RISKS WITH NEURAXIAL ADMINISTRATION; LIFE-THREATENING RESPIRATORY DEPRESSION; RISK OF ADDICTION, ABUSE, AND MISUSE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Risks with Neuraxial Administration

Because of the risk of severe adverse reactions when MITIGO 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 (single) test dose and, as appropriate, for the first several days after catheter implantation [see Warnings and Precautions (5.1)].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of MITIGO. Monitor for respiratory depression, especially during initiation of MITIGO or following a dose increase. Patients must be observed in a fully equipped and staffed environment for at least 24 hours after each test dose and, as indicated, for the first several days after surgery [see Warnings and Precautions (5.2)].

Addiction, Abuse, and Misuse

MITIGO 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 MITIGO, and monitor all patients regularly for the development of these behaviors and conditions [see Warnings and Precautions (5.3)].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of MITIGO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [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 [see Warnings and Precautions (5.5), Drug Interactions (7)]

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

1 INDICATIONS & USAGE

MITIGO is for use in continuous microinfusion devices and indicated only for intrathecal or epidural infusion in the management of intractable chronic pain severe enough to require an opioid analgesic and for which less invasive means of controlling pain are inadequate.

Limitations of Use

Not for single-dose intravenous, intramuscular, or subcutaneous administration due to the risk of overdose. Not for single-dose neuraxial injection because MITIGO is too concentrated for accurate delivery of the smaller doses used in this setting.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

MITIGO 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.

- Because of the risk of delayed respiratory depression, patients should be observed in a fully equipped and staffed environment for at least 24 hours after each test dose and, as indicated, for the first several days after surgery.
- 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 MITIGO 200 mg/20 mL and 500 mg/20 mL (10 and 25 mg/mL, respectively) by the intrathecal route be limited to the lumbar area.
- MITIGO 200 mg/20 mL and 500 mg/20 mL (10 and 25 mg/ml, respectively) should not be used for single-dose neuraxial injection because lower doses can be more reliably administered with the standard preparation of morphine sulfate injection, USP (0.5 and 1 mg/mL).

Candidates for neuraxial administration of MITIGO in a continuous microinfusion device should be hospitalized to provide for adequate patient monitoring during assessment of response to single doses of intrathecal or epidural morphine. Hospitalization should be maintained for several days after surgery involving the infusion device for additional monitoring and adjustment of daily dosage. The facility must be equipped with resuscitative equipment, oxygen, naloxone injection and other resuscitative drugs.

A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir. Before discharge, the patient and attendant(s) should receive instruction in the proper home care of the device and insertion site and in the recognition and practical treatment of an overdose of neuraxial morphine.

Familiarization with the continuous microinfusion device is essential. The desired amount of morphine should be withdrawn from the vial through a microfilter. To minimize risk from glass or other particles, the product must be filtered through a 5 µ (or smaller) microfilter before injecting into the microinfusion device. If dilution is required, 0.9% Sodium Chloride Injection is recommended.

Reservoir filling must be performed by fully trained and qualified personnel, following the directions provided by the device manufacturer. Care should be taken in selecting the proper refill frequency to prevent depletion of the reservoir, which would result in exacerbation of severe pain, onset of opioid withdrawal symptoms, and/or reflux of cerebrospinal fluid into some devices. Strict aseptic technique is required to avoid bacterial contamination and serious infection. Extreme care must be taken to ensure that the needle is properly inserted into the filling port of the device before attempting to refill the reservoir. Injecting the solution into the tissue around the device or (in the case of devices that have more than one port) attempting to inject the refill dose into the direct injection port will result in a large, clinically significant, overdosage to the patient.

Safety and Handling Instructions:

MITIGO is supplied in sealed vials. 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 before opening the amber vials and again for color after removing contents from the vial. Do not use if the solution in the unopened vial contains a precipitate which does not disappear upon shaking. After removal, do not use unless the solution is colorless or pale yellow.

MITIGO is intended for single-dose only. Protect from light, discard any unused portion. Do not heat-sterilize.

2.2 Initial Dosage

The starting dose of MITIGO must be individualized, based upon in-hospital evaluation of the response to serial single-dose epidural or intrathecal bolus injections of regular morphine sulfate injection 0.5 mg/mL or 1 mg/mL, with close observation for analgesic efficacy and adverse effects prior to surgery involving the continuous microinfusion device.

- Use the lowest effective dosage for the shortest duration 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 severity of pain, patient response, prior analgesic treatment experience, 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 MITIGO and adjust the dosage accordingly [see *Warnings and Precautions* (5.2)].

2.3 Dosage for Epidural Administration

The recommended initial epidural dose in patients who are not tolerant to opioids ranges from 3.5 to 7.5 mg/day. 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 10 mg/day. The dose requirements may increase significantly during treatment, frequently to 20-30 mg/day. The upper daily limit for each patient must be individualized.

2.4 Dosage for Intrathecal Administration

The recommended initial lumbar intrathecal dose range in patients with no tolerance to opioids is 0.2 to 1 mg/day. The published range of doses for individuals who have some degree of opioid tolerance varies from 1 to 10 mg/day. The upper daily dosage limit for each patient must be individualized.

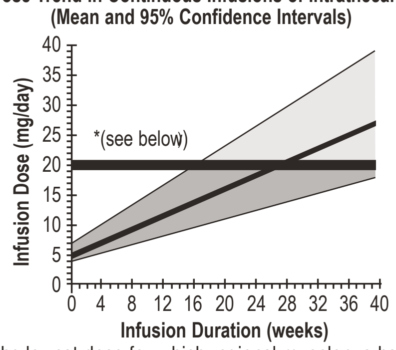
- Intrathecal dosage is usually 1/10 that of epidural dosage.

2.5 Titration and Maintenance of Therapy

Individually titrate MITIGO to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving MITIGO to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see *Warnings and Precautions* (5.3)]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of the increased pain before increasing the MITIGO dosage. Limited experience with continuous intrathecal infusion of morphine has shown that the daily doses have to be increased over time. Although the rate of increase, over time, in the dose required to sustain analgesia is highly variable, an estimate of the expected rate of increase is shown in the following Figure.

Figure: Dose Trend in Continuous Infusions of Intrathecal Morphine (Mean and 95% Confidence Intervals)



*20 mg/day is the lowest dose for which regional myoclonus has been reported. The rate of occurence cannot be estimated.

Doses above 20 mg/day should be employed with caution since they may be associated with a higher likelihood of serious side effects [see *Warnings and Precautions* (5.2, 5.7) and *Adverse Reactions* (6)].

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.6 Discontinuation of MITIGO

When a patient who has been taking MITIGO regularly and may be physically dependent no longer requires therapy with MITIGO, 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 stop MITIGO abruptly in a physically-dependent patient [see *Warnings and Precautions* (5.15), *Drug Abuse and Dependence* (9.3)].

3 DOSAGE FORMS AND STRENGTHS

Injection: 200 mg per 20 mL (10 mg/mL) Preservative-free amber glass single-dose vials

Injection: 500 mg per 20 mL (25 mg/mL) Preservative-free amber glass single-dose vials

4 CONTRAINDICATIONS

MITIGO 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* (5.8)]
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days [see *Warnings and Precautions* (5.9)/*Drug Interactions* (7)]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions* (5.13)]
- Hypersensitivity to morphine (e.g., anaphylaxis) [See *Adverse Reactions* (6)]

Neuraxial administration of MITIGO is contraindicated in patients with:

- Infection at the injection microinfusion site [see *Warnings and Precautions* (5.1)]
- Concomitant anticoagulant therapy [see *Warnings and Precautions* (5.1)]
- Uncontrolled bleeding diathesis [see *Warnings and Precautions* (5.1)]

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 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.

MITIGO 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 MITIGO 200 mg/20 mL and 500 mg/20 mL (10 and 25 mg/mL, respectively) by the intrathecal route be limited to the lumbar area.

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 opioid antagonists, 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 MITIGO, 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 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 MITIGO are essential [see *Dosage and Administration* (2)]. Overestimating the MITIGO dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

IMPROPER OR ERRONEOUS SUBSTITUTION OF MITIGO 200 mg/20 mL and 500 mg/20 mL (10 or 25 mg/mL, respectively) FOR REGULAR MORPHINE SULFATE INJECTION (0.5 or 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 *Dosage and Administration* (2.6)].

5.3 Addiction, Abuse, and Misuse

MITIGO contains morphine, a Schedule II controlled substance. As an opioid, MITIGO 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 MITIGO. 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 MITIGO, and monitor all patients receiving MITIGO 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 MITIGO, but use in such patients necessitates intensive counseling about the risks and proper use of MITIGO 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 MITIGO. 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 vial of MITIGO 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. MITIGO should be subject to rigid accounting, rigorous control of wastage, and restricted access.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of MITIGO 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 [see *Use in Specific Populations* (8.1), *Patient Counseling Information* (17)].

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 MITIGO 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.

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. 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 MITIGO 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), *Patient Counseling Information* (17)].

5.6 Risk of Inflammatory Masses

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 MITIGO via indwelling intrathecal catheter. Patients receiving continuous infusion of MITIGO 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.

5.7 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.

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

The use of MITIGO 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 MITIGO [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 MITIGO and when MITIGO is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions* (5.2)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.9 Interaction with Monoamine Oxidase Inhibitors

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

5.10 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.

5.11 Severe Hypotension

MITIGO 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 MITIGO. In patients with circulatory shock, MITIGO may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of MITIGO in patients with circulatory shock.

5.12 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), MITIGO 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 MITIGO. MITIGO 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* (5.7)]. 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 MITIGO in patients with impaired consciousness or coma.

5.13 Risks of Use in Patients with Gastrointestinal Conditions

MITIGO is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The morphine in MITIGO 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.

5.14 Increased Risks of Seizures in Patients with Seizure Disorders

The morphine in MITIGO 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 MITIGO therapy.

5.15 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients, mixed agonist/antagonist and partial agonist analgesics, including MITIGO. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing MITIGO, gradually taper the dosage [see *Dosage and Administration* (2.6)]. Do not abruptly discontinue MITIGO [see *Drug Abuse and Dependence* (9.3)].

5.16 Risk of Driving and Operating Machinery

MITIGO 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 MITIGO and know how they will react to the medication [see *Patient Counseling Information* (17)].

5.17 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 a 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.

5.18 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 CNS Benzodiazepines or Other Depressants [see *Warnings and Precautions* (5.5)]
- Inflammatory Masses [see *Warnings and Precautions* (5.6)]
- Myoclonic Activity [see *Warnings and Precautions* (5.7)]
- Adrenal Insufficiency [see *Warnings and Precautions* (5.10)]
- Severe Hypotension [see *Warnings and Precautions* (5.11)]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions* (5.13)]
- Seizures [see *Warnings and Precautions* (5.14)]
- Withdrawal [see *Warnings and Precautions* (5.15)]
- Urinary Retention [see *Warnings and Precautions* (5.17)]
- Orthostatic Hypotension [see *Warnings and Precautions* (5.18)]

The following adverse reactions associated with the use of morphine were identified in clinical studies or postmarketing 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 continuous intrathecal or epidural infusion of MITIGO 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.

Genitourinary 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.

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 MITIGO.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see *Clinical Pharmacology* (12.2)].

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with MITIGO.

Table 1. Clinically Significant Drug Interactions with MITIGO

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.
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. Follow patients closely for signs of respiratory depression and sedation [see *Warnings and Precautions* (5.5)].
Examples	Alcohol, benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, psychotropic drugs, antihistamines, neuroleptics, 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.
Intervention	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue MITIGO 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* (5.9)].
Intervention	Do not use MITIGO 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 other opioids (such as oxycodone, hydrocodone, 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 MITIGO 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 MITIGO 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 MITIGO 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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy can cause neonatal opioid withdrawal syndrome [see *Warnings and Precautions* (5.4)]. There are no available data with MITIGO in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. 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.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics 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

MITIGO 200 mg/20 mL and 500 mg/20 mL (10 and 25 mg/mL, respectively) are too highly concentrated for routine use in obstetric neuraxial analgesia. Opioids, including intravenously, epidurally, and intrathecally administered morphine, readily cross the placenta and may produce respiratory depression and psychophysiological 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.

MITIGO is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate.

Opioid analgesics, including MITIGO, 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.

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).

8.2 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 MITIGO, 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 MITIGO and any potential adverse effects on the breastfed infant from MITIGO or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to MITIGO 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

Infertility

Chronic use of opioids 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 MITIGO. 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 MITIGO slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see *Warnings and Precautions* (5.8)].

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 MITIGO epidurally 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

MITIGO contains morphine, a Schedule II controlled drug substance.

9.2 Abuse

MITIGO contains morphine, a substance with a high potential for abuse similar to other opioids. MITIGO can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions* (5.3)].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

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

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"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 health care provider(s).

"Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor 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.

MITIGO, 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.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also 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 opioid usage.

MITIGO should not be abruptly discontinued [see *Dosage and Administration* (2.6)]. If MITIGO is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, 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

Clinical Presentation

Acute overdose with MITIGO 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, 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)].

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 techniques.

The opioid antagonists, naloxone or nalmefene, 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. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose.

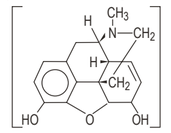
As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary. Patients should be closely observed for evidence of renarcotization.

Because the duration of opioid reversal is expected to be less than the duration of action of morphine in MITIGO, 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.

11 DESCRIPTION

MITIGO (morphine sulfate injection, USP – Preservative-free) is an opioid agonist, available as a sterile, nonpyrogenic, isobaric, high potency solution of morphine sulfate in strengths of 10 mg or 25 mg morphine sulfate per mL, free of antioxidants, preservatives or other potentially neurotoxic additives. MITIGO is intended for use in continuous microinfusion devices for intraspinal administration in the management of pain. 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:



• H_2SO_4 • $5H_2O$

2

$(C_{17}H_{19}NO_3)_2$•H_2SO_4•$5H_2O$ Molecular Weight = 758.83

Morphine sulfate USP is an odorless, white crystalline powder with a bitter taste. 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).

Each mL of MITIGO 200 mg/20 mL contains morphine sulfate, USP 10 mg and sodium chloride 8 mg in Water for Injection, USP. Each mL of MITIGO 500 mg/20 mL contains morphine sulfate, USP 25 mg and sodium chloride 6.25 mg in Water for Injection, USP. If needed, sodium hydroxide and/or sulfuric acid are added for pH adjustment to 4.5. Contains no preservative. Each 20mL vial of MITIGO is intended for SINGLE-DOSE ONLY.

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

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.

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 pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

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.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see *Adverse Reactions* (6)].

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 potent agonist opioids. 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* (2.1)].

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* (2.1, 2.2, 2.6)].

12.3 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 < 1380 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.

13 NONCLINICAL TOXICOLOGY

13.1 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

MITIGO (morphine sulfate injection, USP), is a preservative-free solution, supplied in amber vials for epidural or intrathecal administration via a continuous microinfusion device as follows:

MITIGO 200 mg/20 mL (10 mg/mL) – NDC 66794-160-02: Single-Dose amber vials packaged individually

MITIGO 500 mg/20 mL (25 mg/mL) – NDC 66794-162-02: Single-Dose amber vials packaged individually

MITIGO is supplied in sealed vials. Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water.

PROTECT FROM LIGHT. Keep stored in carton until time of use. Store at 20° - 25°C (68° - 77°F), excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature]. DO NOT FREEZE. MITIGO contains no preservative or antioxidant. Each 20 mL vial of MITIGO is intended for SINGLE-DOSE ONLY. Discard any unused portion. Do not heat-sterilize.

To report SUSPECTED ADVERSE REACTIONS, contact Piramal Critical Care, Inc. at 1-888-822-8431 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

For Product Inquiry call 1-888-822-8431.

17 PATIENT COUNSELING INFORMATION

Addiction, Abuse, and Misuse

Inform patients that the use of MITIGO, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see *Warnings and Precautions* (5.3)]. Instruct patients not to share MITIGO with others and to take steps to protect MITIGO from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting MITIGO or when the dosage is increased, and that it can occur even at recommended dosages [see *Warnings and Precautions* (5.2)]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if MITIGO is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see *Warnings and Precautions* (5.5), *Drug Interactions* (7)].

Serotonin Syndrome

Inform patients that MITIGO could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications [see *Drug Interactions* (7)].

MAOI Interaction

Inform patients not to take MITIGO while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking MITIGO [see *Warnings and Precautions* (5.9), *Drug Interactions* (7)].

Hypotension

Inform patients that MITIGO may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see *Warnings and Precautions* (5.11)].

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in MITIGO. Advise patients how to recognize such a reaction and when to seek medical attention [see *Contraindications* (4), *Adverse Reactions* (6)].

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of MITIGO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.1)].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that MITIGO can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [see *Use in Specific Populations* (8.3)].

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [see *Use in Specific Populations* (8.2)].

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see *Adverse Reactions* (6)].

Driving or Operating Heavy Machinery

Inform patients that MITIGO may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advice patients not to perform such tasks until they know how they will react to the medication [see *Warnings and Precautions* (5.16)].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see *Adverse Reactions* (6)].

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