

MORPHINE SULFATE- morphine sulfate suppository

Padagis US LLC

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

MORPHINE SULFATE suppositories, for rectal use, CII

Initial U.S. Approval: 1941

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

See full prescribing information for complete boxed warning.

- **Morphine sulfate suppositories expose users to risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)**
- **Accidental exposure of morphine sulfate suppositories, especially by children, can result in a fatal overdose of opium. (5.2)**
- **Prolonged use of morphine sulfate suppositories 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. (5.3)**
- **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. (5.4, 7)**

RECENT MAJOR CHANGES

Boxed Warning 11/2018

Indications and Usage (1) 11/2018

Dosage and Administration (2) 11/2018

Contraindications (4) 11/2018

Warnings and Precautions (5) 11/2018

INDICATIONS AND USAGE

Morphine sulfate suppositories is an opioid agonist indicated for the management of acute and chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve morphine sulfate suppositories for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]: (1)

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

-----DOSAGE AND ADMINISTRATION-----

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Usual adult dosage of morphine sulfate suppositories is 10 to 20 mg every 4 hours as needed. (2.2)
- Do not stop morphine sulfate suppositories abruptly in a physically-dependent patient. (2.4)

-----DOSAGE FORMS AND STRENGTHS-----

Suppositories: (3)

- 5 mg
- 10 mg
- 20 mg
- 30 mg

-----CONTRAINDICATIONS-----

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or 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 to morphine. (4)

-----WARNINGS AND PRECAUTIONS-----

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.5)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of morphine sulfate suppositories in patients with circulatory shock. (5.8)
- 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 morphine sulfate suppositories in patients with impaired consciousness or coma. (5.9)

-----ADVERSE REACTIONS-----

Most common adverse reactions are constipation, nausea, somnolence, lightheadedness, dizziness, sedation, vomiting, sweating. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

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

-----USE IN SPECIFIC POPULATIONS-----

Pregnancy: May cause fetal harm. (8.1) (8)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY

DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

Morphine sulfate suppositories expose 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 sulfate suppositories, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions (5.1)*].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of morphine sulfate suppositories. Monitor for respiratory depression, especially during initiation of morphine sulfate suppositories or following a dose increase [see *Warnings and Precautions (5.2)*].

Accidental Exposure

Accidental exposure of even one dose of morphine sulfate suppositories, especially by children, can result in a fatal overdose of morphine [see *Warnings and Precautions (5.2)*].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of morphine sulfate suppositories 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 (5.3)*].

Risks From Concomitant Use With Alcohol, 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 (5.4), Drug Interactions (7)*].

- Reserve concomitant prescribing of morphine sulfate suppositories 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 AND USAGE

Morphine sulfate suppositories are indicated for the management of acute and chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see *Warnings and Precautions (5.1)*], reserve morphine sulfate suppositories for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Morphine sulfate suppositories are available in four strengths: 5 mg per suppository, 10 mg per suppository, 20 mg per suppository, and 30 mg per suppository.

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5)*].

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 (5.1)*].

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with morphine sulfate suppositories and adjust the dosage accordingly [see *Warnings and Precautions (5.2)*].

2.2 Initial Dosage

Initiating Treatment with Morphine Sulfate Suppositories

Initiate treatment with morphine sulfate suppositories in a dosing range of 10 – 20 mg, rectally, every 4 hours.

Conversion from Other Opioids to Morphine Sulfate Suppositories

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised with determining the total daily dosage of morphine sulfate suppositories. It is safer to underestimate a patient's 24-hour morphine sulfate dosage than to overestimate the 24-hour dosage and manage an adverse reaction due to overdose.

Conversion from Morphine Sulfate Suppositories to Extended-Release Morphine

The relative bioavailability of morphine sulfate suppositories compared to extended-release morphine is unknown, so conversion to extended-release drug product must be accompanied by close observation for signs of excessive sedation and respiratory

depression.

2.3 Titration and Maintenance of Therapy

Individually titrate morphine sulfate suppositories to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving morphine sulfate suppositories 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 (5.1)*]. 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 increased pain before increasing the morphine sulfate suppositories dosage. 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.

2.4 Discontinuation of Morphine Sulfate Suppositories

When a patient who has been taking morphine sulfate suppositories regularly and may be physically dependent no longer requires therapy with morphine sulfate suppositories, taper the dose gradually, by 25% to 50% every 2 to 4 days, 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 abruptly discontinue morphine sulfate suppositories in a physically-dependent patient [see *Warnings and Precautions (5.12)*, *Drug Abuse and Dependence (9.3)*].

3 DOSAGE FORMS AND STRENGTHS

Morphine Sulfate Suppositories are available in four strengths:

- 5 mg per suppository
- 10 mg per suppository
- 20 mg per suppository
- 30 mg per suppository

4 CONTRAINDICATIONS

Morphine sulfate suppositories are 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 (5.5)*]
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days [see *Warnings and Precautions (5.6)*, *Drug Interactions (7)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions (5.10)*]

- Hypersensitivity to morphine (e.g., anaphylaxis) [*see Adverse Reactions (6)*]

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Morphine sulfate suppositories contain morphine, a Schedule II controlled substance. As an opioid, morphine sulfate suppositories expose users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed morphine sulfate. 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 sulfate suppositories, and monitor all patients receiving morphine sulfate suppositories 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 sulfate suppositories, but use in such patients necessitates intensive counseling about the risks and proper use of morphine sulfate suppositories along with the intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing morphine sulfate suppositories. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*]. 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.

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 (CO₂) 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 sulfate suppositories, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of morphine sulfate suppositories.

To reduce the risk of respiratory depression, proper dosing and titration of morphine sulfate suppositories are essential [*see Dosage and Administration (2)*]. Overestimating the morphine sulfate suppositories dosage when converting patients from another

opioid product can result in a fatal overdose with the first dose.

Accidental exposure of even one dose of morphine sulfate suppositories, especially by children, can result in respiratory depression and death due to an overdose of morphine.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of morphine sulfate suppositories 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)*].

5.4 Risks from Concomitant Use with Alcohol, Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of morphine sulfate suppositories 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.

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 morphine sulfate suppositories 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)* and *Patient Counseling Information (17)*].

5.5 Life-Threatening Respiratory Depression in Patients with Chronic

Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of morphine sulfate suppositories 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: Morphine sulfate suppositories-treated 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 dosages of morphine sulfate suppositories [see *Warnings and Precautions (5.2)*].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see *Warnings and Precautions (5.2)*].

Monitor such patients closely, particularly when initiating and titrating morphine sulfate suppositories and when morphine sulfate suppositories 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.

5.6 Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, including respiratory depression, coma, and confusion. Morphine sulfate suppositories should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

5.7 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.

5.8 Severe Hypotension

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

Avoid the use of morphine sulfate suppositories in patients with circulatory shock.

5.9 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 CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), morphine sulfate suppositories may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with morphine sulfate suppositories.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of morphine sulfate suppositories in patients with impaired consciousness or coma.

5.10 Risks of Use in Patients with Gastrointestinal Conditions

Morphine sulfate suppositories is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The morphine in morphine sulfate suppositories 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.

5.11 Increased Risk of Seizures in Patients with Seizure Disorders

The morphine in morphine sulfate suppositories may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during morphine sulfate suppositories therapy.

5.12 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 sulfate suppositories. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [*see Drug Interactions (7)*].

When discontinuing morphine sulfate suppositories, gradually taper the dosage [*see Dosage and Administration (2.4)*]. Do not abruptly discontinue morphine sulfate suppositories [*see Drug Abuse and Dependence (9.3)*].

5.13 Risks of Driving and Operating Machinery

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

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in

other sections:

- Addiction, Abuse, and Misuse [see *Warnings and Precautions (5.1)*]
- Life-Threatening Respiratory Depression [see *Warnings and Precautions (5.2)*]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions (5.3)*]
- Interactions with Benzodiazepine or Other CNS Depressants [see *Warnings and Precautions (5.4)*]
- Adrenal Insufficiency [see *Warnings and Precautions (5.7)*]
- Severe Hypotension [see *Warnings and Precautions (5.8)*]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions (5.10)*]
- Seizures [see *Warnings and Precautions (5.11)*]
- Withdrawal [see *Warnings and Precautions (5.12)*]

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.

Serious adverse reactions associated with morphine use included: respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The common adverse reactions seen on initiation of therapy with morphine were dose-dependent and were typical opioid-related adverse reactions. The most frequent of these included constipation, nausea, and somnolence. Other commonly observed adverse reactions included: lightheadedness, dizziness, sedation, vomiting, and sweating. The frequency of these events depended upon several factors including clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual.

Other less frequently observed adverse reactions from opioid analgesics, including morphine sulfate included:

Body as a Whole: malaise, withdrawal syndrome

Cardiovascular System: bradycardia, hypertension, hypotension, palpitations, syncope, tachycardia

Digestive System: anorexia, biliary pain, dyspepsia, dysphagia, gastroenteritis, abnormal liver function tests, rectal disorder, thirst

Endocrine: hypogonadism

Hemic and Lymphatic System: anemia, thrombocytopenia

Metabolic and Nutritional Disorders: edema, weight loss

Musculoskeletal: skeletal muscle rigidity, decreased bone mineral density

Nervous System: abnormal dreams, abnormal gait, agitation, amnesia, anxiety, ataxia, confusion, convulsions, coma, delirium, depression, dry mouth, euphoria, hallucinations, lethargy, nervousness, abnormal thinking, tremor, vasodilation, vertigo, headache

Respiratory System: hiccup, hypoventilation, voice alteration

Skin and Appendages: dry skin, urticaria, pruritus

Special Senses: amblyopia, eye pain, taste perversion

Urogenital System: abnormal ejaculation, dysuria, impotence, decreased libido, oliguria, urinary retention or hesitancy, anti-diuretic effect, amenorrhea

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 sulfate suppositories.

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 morphine sulfate suppositories.

Table 1: Clinically Significant Drug Interactions with Morphine Sulfate Suppositories

Alcohol, Benzodiazepines and Other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	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 <i>Warnings and Precautions (5.4)</i>].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue morphine sulfate suppositories if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that effect the

serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), 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 (5.2, 5.6)*]

Intervention: Do not use morphine sulfate suppositories in patients taking MAOIs or within 14 days of stopping such treatment.

Examples: phenelzine, tranylcypromine, linezolid

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Clinical Impact: May reduce the analgesic effect of morphine sulfate suppositories 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 sulfate suppositories and/or the muscle relaxant as necessary.

Cimetidine

Clinical Impact: The concomitant use of morphine 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 morphine sulfate suppositories are used concomitantly with cimetidine.

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 sulfate suppositories are used concomitantly with anticholinergic drugs.

P-Glycoprotein (P-gp) Inhibitors

Clinical Impact: The concomitant use of P-gp inhibitors can increase the exposure to morphine by twofold and can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Intervention: Monitor patients for signs of respiratory depression that may be

	greater than otherwise expected and decrease the dosage of morphine sulfate suppositories and/or the P-gp inhibitor as necessary.
<i>Examples:</i>	quinidine, verapamil

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 (5.3)*]. There are no available data with morphine sulfate suppositories 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 to 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 to 4% and 15 to 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 (5.3)*].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psychophysiological effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Morphine sulfate suppositories are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including morphine sulfate suppositories, 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 to 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 to 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 sternbrae, 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 to 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 morphine sulfate suppositories 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 sulfate suppositories and any potential adverse effects on the breastfed infant from morphine sulfate suppositories or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to morphine sulfate suppositories 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

The safety and effectiveness and the pharmacokinetics of morphine sulfate suppositories in pediatric patients below the age of 18 have not been established.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to morphine. In general, use caution when selecting a dose 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 sulfate suppositories slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see *Warnings and Precautions (5.5)*].

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 Impairment

Morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Start these patients with a lower than usual dosage of morphine sulfate suppositories and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension [see *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

Morphine pharmacokinetics are altered in patients with renal failure. Start these patients with a lower than usual dosage of morphine sulfate suppositories and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension [see Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Morphine sulfate suppositories contains morphine, a Schedule II controlled substance.

9.2 Abuse

Morphine sulfate suppositories contain morphine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone, and tapentadol. Morphine sulfate suppositories can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions* (5.1)].

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 healthcare 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.

Morphine sulfate suppositories, 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 Sulfate Suppositories

Morphine sulfate suppositories are for rectal use only. Abuse of morphine sulfate suppositories poses a risk of overdose and death. The risk is increased with concurrent abuse of morphine sulfate suppositories with alcohol and other central nervous system depressants. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during 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.

Morphine sulfate suppositories should not be abruptly discontinued in a physically-dependent patient [see *Dosage and Administration (2.4)*]. If morphine sulfate suppositories are 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 morphine sulfate suppositories 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.

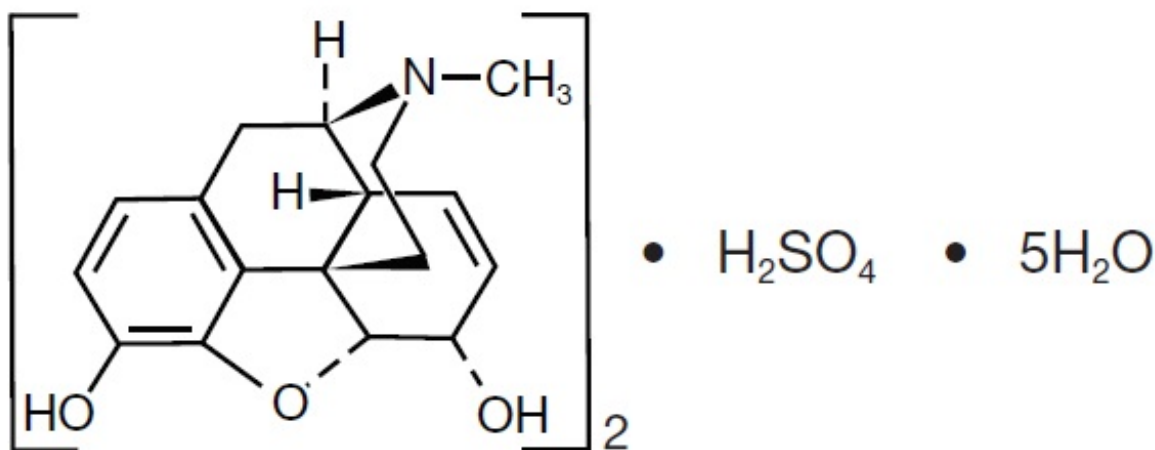
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of morphine in morphine sulfate suppositories, 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 initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

Morphine sulfate suppositories are an opioid agonist, available in 5 mg, 10 mg, 20 mg, and 30 mg strengths for rectal administration. The chemical name is morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-, (5a,6a)-, sulfate (2:1) (salt), pentahydrate. The molecular weight is 758. Its molecular formula is $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$, and it has the following chemical structure:



Morphine sulfate USP is a white to off-white crystalline powder or a fine white to light yellow powder. It is soluble in water and slightly soluble in 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).

The inactive ingredients in morphine sulfate suppositories include: butylated hydroxyanisole, butylated hydroxytoluene, colloidal silicon dioxide, glyceryl monostearate, hydrogenated vegetable oil, polysorbate 80.

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 pathognomonic (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.

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, 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, 2.3)*].

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, 2.3)*].

12.3 Pharmacokinetics

Absorption

Morphine, when administered as morphine sulfate is about two-thirds absorbed from the gastrointestinal tract with the maximum analgesic effect occurring 60 minutes post-administration. The oral bioavailability of morphine sulfate is less than 40% and shows large inter-individual variability due to extensive pre-systemic metabolism.

Distribution

Once absorbed, morphine sulfate is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Although the primary site of action is the CNS, only small quantities cross the blood-brain barrier. Morphine sulfate also crosses the placental membranes and has been found in breast milk. The volume of distribution of morphine sulfate is approximately 1 to 6 L/kg, and morphine sulfate is 20 to 35% reversibly bound to plasma proteins.

Elimination

Metabolism: The major pathway of morphine sulfate detoxification is conjugation, either with D-glucuronic acid to produce glucuronides or with sulfuric acid to produce morphine-3-etheral sulfate. While a small fraction (less than 5%) of morphine sulfate is

demethylated, virtually all morphine sulfate is converted by hepatic metabolism to the 3- and 6-glucuronide metabolites (M3G and M6G; about 50% and 15%, respectively). M6G has been shown to have analgesic activity but crosses the blood-brain barrier poorly, while M3G has no significant analgesic activity.

Excretion: Most of a dose of morphine sulfate is excreted in urine as M3G and M6G, with elimination of morphine sulfate occurring primarily as renal excretion of M3G. Approximately 10% of the dose is excreted unchanged in urine. A small amount of glucuronide conjugates are excreted in bile, with minor enterohepatic recycling. Seven to 10% of administered morphine sulfate is excreted in the feces.

The mean adult plasma clearance is approximately 20 to 30 mL/min/kg. The effective terminal half-life of morphine sulfate after IV administration is reported to be approximately 2 hours. In some studies involving longer periods of plasma sampling, a longer terminal half-life of morphine sulfate of about 15 hours was reported.

Specific Populations

Race/Ethnicity: There may be some pharmacokinetic differences associated with race. In one published study, Chinese subjects given intravenous morphine sulfate had a higher clearance when compared to Caucasian subjects (1852 +/- 116 mL/min compared to 1495 +/- 80 mL/min).

Sex: While evidence of greater post-operative morphine sulfate 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 sulfate, 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. 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.

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).

Exposure of adolescent male rats to morphine has been associated with delayed sexual maturation and 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

Morphine Sulfate Suppositories are white to cream torpedo shaped suppositories

Strength	Carton Count	NDC Number
5 mg	12 suppositories	0574-7110-12
10 mg	12 suppositories	0574-7112-12
20 mg	12 suppositories	0574-7114-12
30 mg	12 suppositories	0574-7116-12

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Addiction, Abuse, and Misuse

Inform patients that the use of morphine sulfate suppositories, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose

and death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share morphine sulfate suppositories with others and to take steps to protect morphine sulfate suppositories 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 morphine sulfate suppositories 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.

Accidental Exposure

Inform patients that accidental exposure (including ingestion), especially by children, may result in respiratory depression or death [see *Warnings and Precautions (5.2)*]. Instruct patients to take steps to store morphine sulfate suppositories securely and to dispose of unused morphine sulfate suppositories by flushing the unused suppositories down the toilet.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if morphine sulfate suppositories are 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 (5.4)*, *Drug Interactions (7)*].

Serotonin Syndrome

Inform patients that opioids 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 morphine sulfate suppositories while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking morphine sulfate suppositories [see *Warnings and Precautions (5.6)*, *Drug Interactions (7)*].

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see *Warnings and Precautions (5.7)*].

Hypotension

Inform patients that morphine sulfate suppositories 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 (5.8)*].

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in morphine sulfate suppositories. 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 morphine sulfate suppositories during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.3), Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity: Inform female patients of reproductive potential that morphine sulfate suppositories can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

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 Use in Specific Populations (8.3)*].

Driving or Operating Heavy Machinery

Inform patients that morphine sulfate suppositories may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [*see Warnings and Precautions (5.13)*].

Constipation

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

Disposal of Unused Morphine Sulfate Suppositories

Advise patients to dispose of unused morphine suppositories by flushing down the toilet.

Medication Guide

Morphine Sulfate (mor' feen sul' fate) Suppositories, CII

Morphine Sulfate Suppositories are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage short term (acute) and long term (chronic) pain severe enough to require an opioid pain medicine, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction,

abuse, and misuse that can lead to death.

Important information about morphine sulfate:

- Get emergency help right away if you take too many morphine sulfate suppositories (overdose). When you first start taking morphine sulfate suppositories, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking morphine sulfate suppositories with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your morphine sulfate suppositories. They could die from taking it. Store morphine sulfate suppositories away from children and in a safe place to prevent stealing or abuse. Selling or giving away morphine sulfate suppositories is against the law.

Do not take morphine sulfate suppositories if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.
- an allergy to morphine

Before taking morphine sulfate suppositories, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of morphine sulfate suppositories during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Morphine sulfate passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking morphine sulfate suppositories with certain other medicines can cause serious side effects that could lead to death.

When taking morphine sulfate suppositories:

- Do not change your dose. Take morphine sulfate suppositories exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 4 hours as needed for pain. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.

- If you have been taking morphine sulfate suppositories regularly, do not stop taking morphine sulfate suppositories without talking to your healthcare provider.
- After you stop taking morphine sulfate suppositories, flush unused morphine sulfate suppositories down the toilet.

While taking morphine sulfate suppositories DO NOT:

- Drive or operate heavy machinery, until you know how morphine sulfate suppositories affects you. Morphine sulfate suppositories can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with morphine sulfate suppositories may cause you to overdose and die.

The possible side effects of morphine sulfate suppositories:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of morphine sulfate suppositories. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

For more information go to dailymed.nlm.nih.gov.

Manufactured by: Perrigo, Minneapolis, MN 55427, www.perrigo.com or please call 1-866-634-9120

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Manufactured By

Perrigo®

Minneapolis, MN 55427

www.perrigo.com

Rev 11-18 A

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1R600 RC J1

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - 5 mg Suppository Carton

Rx Only

Morphine Sulfate Suppositories 5 mg

FOR RECTAL USE ONLY

Warning: May be habit forming.

Dispense the accompanying Medication Guide to each patient

12 Suppositories

UNIT DOSE



The following image is a placeholder representing the product identifier that is either affixed or imprinted on the drug package label during the packaging operation.

S/N [insert product's serial number]
Lot [insert product's lot number]
Exp [insert product's expiration date]

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - 10 mg Suppository Carton

Rx Only

Morphine Sulfate Suppositories 10 mg

FOR RECTAL USE ONLY

Warning: May be habit forming.

Dispense the accompanying Medication Guide to each patient

12 Suppositories

UNIT DOSE



The following image is a placeholder representing the product identifier that is either affixed or imprinted on the drug package label during the packaging operation.

S/N [insert product's serial number]
 Lot [insert product's lot number]
 Exp [insert product's expiration date]

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - 20 mg Suppository Carton

Rx Only

Morphine Sulfate Suppositories 20 mg

FOR RECTAL USE ONLY

Warning: May be habit forming.

Dispense the accompanying Medication Guide to each patient

12 Suppositories

UNIT DOSE



The following image is a placeholder representing the product identifier that is either affixed or imprinted on the drug package label during the packaging operation.

S/N [insert product's serial number] Lot [insert product's lot number] Exp [insert product's expiration date]

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - 30 mg Suppository Carton

Rx Only

Morphine Sulfate Suppositories 30 mg

FOR RECTAL USE ONLY

Warning: May be habit forming.

Dispense the accompanying Medication Guide to each patient

12 Suppositories

UNIT DOSE



The following image is a placeholder representing the product identifier that is either affixed or imprinted on the drug package label during the packaging operation.

S/N [insert product's serial number]
Lot [insert product's lot number]
Exp [insert product's expiration date]

MORPHINE SULFATE

morphine sulfate suppository

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0574-7110
Route of Administration	RECTAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MORPHINE SULFATE (UNII: X3P646A2J0) (MORPHINE - UNII:76I7G6D29C)	MORPHINE SULFATE	5 mg

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
GLYCERYL MONOSTEARATE (UNII: 230OU9XXE4)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
HYDROGENATED PALM KERNEL OIL (UNII: FM8D1RE2VP)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0574-7110-12	12 in 1 BOX	09/01/1990	
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Unapproved drug other		09/01/1990	

MORPHINE SULFATE

morphine sulfate suppository

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0574-7112
Route of Administration	RECTAL	DEA Schedule	CII

Active Ingredient/Active Moiety				
Ingredient Name			Basis of Strength	Strength
MORPHINE SULFATE (UNII: X3P646A2J0) (MORPHINE - UNII:76I7G6D29C)			MORPHINE SULFATE	10 mg
Inactive Ingredients				
Ingredient Name				Strength
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)				
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)				
GLYCERYL MONOSTEARATE (UNII: 230OU9XXE4)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
POLYSORBATE 80 (UNII: 6OZP39ZG8H)				
HYDROGENATED PALM KERNEL OIL (UNII: FM8D1RE2VP)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0574-7112-12	12 in 1 BOX	09/01/1990	
1		1 in 1 PACKET; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
Unapproved drug other			09/01/1990	

MORPHINE SULFATE

morphine sulfate suppository

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0574-7114
Route of Administration	RECTAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name			Basis of Strength	Strength
MORPHINE SULFATE (UNII: X3P646A2J0) (MORPHINE - UNII:76I7G6D29C)			MORPHINE SULFATE	20 mg

Inactive Ingredients

Ingredient Name				Strength
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)				

BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)
GLYCERYL MONOSTEARATE (UNII: 230OU9XXE4)
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)
POLYSORBATE 80 (UNII: 6OZP39ZG8H)
HYDROGENATED PALM KERNEL OIL (UNII: FM8D1RE2VP)

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0574-7114-12	12 in 1 BOX	09/01/1990	
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Unapproved drug other		09/01/1990	

MORPHINE SULFATE

morphine sulfate suppository

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0574-7116
Route of Administration	RECTAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MORPHINE SULFATE (UNII: X3P646A2J0) (MORPHINE - UNII:76I7G6D29C)	MORPHINE SULFATE	30 mg

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
GLYCERYL MONOSTEARATE (UNII: 230OU9XXE4)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
HYDROGENATED PALM KERNEL OIL (UNII: FM8D1RE2VP)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
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#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0574-7116-12	12 in 1 BOX	09/01/1990	
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Unapproved drug other		09/01/1990	

Labeler - Padagis US LLC (967694121)

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Padagis US LLC