MORPHINE SULFATE- morphine sulfate tablet
RedPharm Drug, Inc.

Morphine Sulfate IR 15mg tabs

BOXED WARNING SECTION

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Addiction, Abuse, and Misuse

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

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see *Warnings and Precautions (5.2)*]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to:

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of morphine sulfate tablets. Monitor for respiratory depression, especially during initiation of morphine sulfate tablets or following a dose increase *[see Warnings and Precautions (5.3)]* .

Accidental Ingestion

Accidental ingestion of even one dose of morphine sulfate tablets, especially by children, can result in a fatal overdose of morphine *[see Warnings and Precautions (5.3)]* .

Neonatal Opioid Withdrawal Syndrome

Prolonged use of morphine sulfate tablets 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 morphine sulfate tablets 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 tablets 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 tablets 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

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 to 72 hours of initiating therapy and following dosage increases with morphine sulfate and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]* .

2.2 Initial Dosage

Use of Morphine Sulfate Tablets as the First Opioid Analgesic (Opioid-naïve or Opioid-non-tolerant patients):

Initiate treatment with morphine sulfate tablets in a dosing range of 15 mg to 30 mg every 4 hours as needed for pain.

Conversion from Parenteral Morphine to Morphine Sulfate Tablets:

For conversion from parenteral morphine to morphine sulfate tablets, anywhere from 3 to 6 mg of oral morphine sulfate may be required to provide pain relief equivalent to 1 mg of parenteral morphine.

Conversion from Other Opioids to Morphine Sulfate Tablets:

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of morphine sulfate tablets. It is safer to underestimate a patient's 24-hour morphine sulfate tablets dosage than to overestimate the 24-hour morphine sulfate tablets dosage and manage an adverse reaction due to overdose. Initiate dosing using morphine sulfate tablets 15 mg to 30 mg every 4 hours.

Conversion from Morphine Sulfate Tablets to Extended-Release Morphine:

For a given dose, the same total amount of morphine sulfate is available from morphine sulfate tablets and extended-release morphine formulations. The extended duration of release of morphine sulfate from extended-release formulations results in reduced maximum and increased minimum plasma morphine sulfate concentrations than with shorter acting morphine sulfate products. Conversion from morphine sulfate tablets to the same total daily dose of an extended-release formulation could lead to excessive sedation at peak serum levels. Therefore, conversion to extended-release morphine formulations 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 tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving morphine sulfate tablets 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 tablets 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 Safe Reduction or Discontinuation of Morphine Sulfate Tablets

Do not abruptly discontinue morphine sulfate tablets in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking morphine sulfate tablets, there are a variety of factors

that should be considered, including the dose of morphine sulfate tablets the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on morphine sulfate tablets who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on morphine sulfate tablets who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain

management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.3)]* .

3 DOSAGE FORMS AND STRENGTHS

Morphine sulfate tablets are supplied as:

15 mg: white, round, flat-faced, beveled edge tablet; one side scored and one side debossed "15" and "273".

30 mg: white, round, flat-faced, beveled edge tablet; one side scored and one side debossed "30" and "274".

4 CONTRAINDICATIONS

Morphine sulfate tablets are contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]* .
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.6)]* .
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Warnings and Precautions (5.7), Drug Interactions (7)]* .
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.11)]* .
- Hypersensitivity to morphine (e.g., anaphylaxis) *[see Adverse Reactions (6)]* .

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Morphine sulfate tablets contain morphine, a Schedule II controlled substance. As an opioid, morphine sulfate tablets 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 tablets, and monitor all patients receiving morphine sulfate tablets for the development of these behaviors or 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 tablets but use in such patients necessitates intensive counseling about the risks and proper use of morphine sulfate tablets along with 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 tablets. 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 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: https://www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.3 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 . Carbon dioxide (CO) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. 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 morphine sulfate tablets, 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 tablets.While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of morphine sulfate tablets, 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 tablets.

To reduce the risk of respiratory depression, proper dosing and titration of morphine sulfate tablets are essential . Overestimating the morphine sulfate tablets dosage when converting patients from another opioid product can result in a fatal overdose with the first dose. To reduce the risk of respiratory depression, proper dosing and titration of morphine sulfate tablets are essential *[see Dosage and Administration (2.2, 2.3)]* . Overestimating the morphine sulfate tablets dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

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

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 (2.4)].*

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of morphine sulfate tablets 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 the concomitant use of morphine sulfate tablets 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 tablets are 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 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of morphine sulfate tablets 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 tablets-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 tablets *[see Warnings and Precautions (5.3)]* .

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 (5.3)]* .

Monitor such patients closely, particularly when initiating and titrating morphine sulfate tablets and when morphine sulfate tablets are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.5)]* . Alternatively, consider the use of non-opioid analgesics in these patients.

5.7 Interaction with Monoamine Oxidase Inhibitors

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

5.8 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.

5.9 Severe Hypotension

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

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

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), morphine sulfate tablets may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with morphine sulfate tablets.

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

5.11 Risks of Use in Patients with Gastrointestinal Conditions

Morphine sulfate tablets are contraindicated in patients with gastrointestinal obstruction, including paralytic ileus.

The morphine in morphine sulfate tablets 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.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders

The morphine in morphine sulfate tablets 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 tablets therapy.

5.13 Withdrawal

Do not abruptly discontinue morphine sulfate tablets in a patient physically dependent on opioids. When discontinuing morphine sulfate tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of morphine in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.4), Drug Abuse and Dependence (9.3)].*

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

5.14 Risks of Driving and Operating Machinery

Morphine sulfate tablets 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 tablets 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 (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions with Benzodiazepine or Other CNS Depressants *[see Warnings and Precautions (5.5)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.8)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Withdrawal *[see Warnings and Precautions (5.13)]*

The following adverse reactions associated with the use of morphine were identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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: 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 tablets.

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

To report SUSPECTED ADVERSE REACTIONS, contact Upsher-Smith Laboratories, LLC at 1-855-899-9180 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with morphine sulfate tablets.

Table 1: Clinically Significant Drug Interactions with Morphine Sulfate Tablets

Benzodiazepines and 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.
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:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, 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 morphine sulfate tablets 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 (5.7)].
Intervention:	Do not use morphine sulfate tablets 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 tablets 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 tablets 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 tablets 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 tablets 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 two-fold 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 tablets and/or the P-gp inhibitor as necessary.
Examples	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 (5.4)]* . There are no available data with morphine sulfate tablets 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 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 signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]* .

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

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 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 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 tablets 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 tablets and any potential adverse effects on the breastfed infant from morphine sulfate tablets or from the underlying maternal condition.

Clinical Considerations:

Monitor infants exposed to morphine sulfate tablets 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 tablets 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 tablets slowly in geriatric patients and monitor closely for signs of respiratory depression *[see Warnings and Precautions (5.6)]* . 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 tablets and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3)].*

8.7 Renal Impairment

Morphine sulfate pharmacokinetics are altered in patients with renal failure. Start these patients with a lower than usual dosage of morphine sulfate tablets 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 tablets contain morphine, a Schedule II controlled substance.

9.2 Abuse

Morphine sulfate tablets contains morphine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone, and tapentadol. Morphine sulfate tablets can be abused and are 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 carry 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.

Morphine sulfate tablets, 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 Tablets:

Morphine sulfate tablets are for oral use only. Abuse of morphine sulfate tablets poses a risk of overdose and death. The risk is increased with concurrent abuse of morphine sulfate tablets 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 is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting 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.

Do not abruptly discontinue morphine sulfate tablets in a patient physically dependent on opioids. Rapid tapering of morphine sulfate tablets in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing morphine sulfate tablets, gradually taper the dosage using a patient-specific plan that considers the following: the dose of morphine sulfate tablets the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.4), Warnings and Precautions (5.13)].* 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 tablets 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.

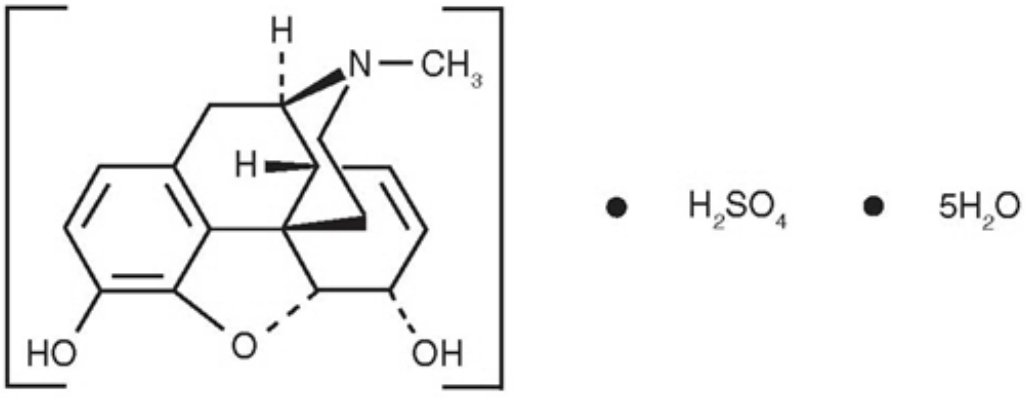
Because the duration of opioid reversal is expected to be less than the duration of action of morphine in morphine sulfate tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist

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 tablets are an opioid agonist, available in 15 mg and 30 mg for oral administration. Chemically, morphine sulfate is 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate. 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). 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:



Each tablet contains 15 or 30 mg of morphine sulfate, USP and the following inactive ingredients: colloidal silicon dioxide, microcrystalline cellulose, pregelatinized starch, and stearic acid.

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, 2.2)]* .

Concentration–Adverse Reaction Relationships:

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

Administration of the 30 mg morphine sulfate tablet and 30 mg morphine sulfate oral solution every six hours for 5 days resulted in a comparable 24-hour exposure (AUC). The steady-state levels were achieved within 48 hours for both tablets and solution. The mean steady state C_{max} values were about 78 and 58 ng/mL for tablets and solution, respectively.

Food Effects: When morphine sulfate 30 mg tablet was administered 30 minutes after ingesting a high fat/high calorie meal, there was no change in the extent of absorption (AUC) of morphine sulfate. There was, however, an increase in the median T_{max} from 0.5 to 0.75 hours and an 11% decrease in C_{max}. The tablet can be administered without regard to meals.

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. The AUC is increased, and clearance is decreased and the metabolites, M3G and M6G, may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.

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 Tablets

15 mg tablet: white, round, flat-faced, beveled edge tablet; one side scored and one side debossed "15" and "273".

Bottles of 100 with child-resistant closure, NDC 0832-0273-11

30 mg tablet: white, round, flat-faced, beveled edge tablet; one side scored and one side debossed "30" and "274".

Bottles of 100 with child-resistant closure, NDC 0832-0274-11

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container with a child-resistant closure as defined in the USP.

PROTECT FROM MOISTURE.

Store morphine sulfate tablets securely and dispose of properly *[see Patient Counseling Information (17)].*

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Storage and Disposal:

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store morphine sulfate tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home *[see Warnings and Precautions (5.1, 5.3), Drug Abuse and Dependence (9.2)].* Inform patients that leaving morphine sulfate tablets unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused morphine sulfate tablets should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse:

Inform patients that the use of morphine sulfate tablets, 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 tablets with others and to take steps to protect morphine sulfate 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 tablets or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.3)]* . Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion:

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]* .

Interactions with Benzodiazepines and Other CNS Depressants:

Inform patients and caregivers that potentially fatal additive effects may occur if morphine sulfate tablets 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 (5.5), 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 tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking morphine sulfate

tablets *[see Warnings and Precautions (5.7), 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 (5.8)].*

Important Administration Instructions:

Instruct patients how to properly take morphine sulfate tablets. Advise patients not to adjust the dose of morphine sulfate without consulting with a physician or other healthcare professional.

Important Discontinuation Instructions:

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue morphine sulfate tablets without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.4)].*

Hypotension:

Inform patients that morphine sulfate tablets 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 (5.9)]* .

Anaphylaxis:

Inform patients that anaphylaxis have been reported with ingredients contained in morphine sulfate tablets. 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 patients of reproductive potential that prolonged use of morphine sulfate tablets 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 morphine sulfate tablets 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 Adverse Reactions (6)].*

Driving or Operating Heavy Machinery:

Inform patients that morphine sulfate tablets 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 (5.14)]* .

Constipation:

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

Manufactured by
UPSHER-SMITH LABORATORIES, LLC
Maple Grove, MN 55369

Revised 1119

Medication Guide
MORPHINE SULFATE (mor´ feen sul´ fate) Tablets, CII

Morphine sulfate tablets 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 tablets:

- **Get emergency help right away if you take too much morphine sulfate tablets (overdose)**. When you first start taking morphine sulfate tablets, 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 tablets 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 tablets. They could die from taking it. Selling or giving away morphine sulfate tablets is against the law.
- Store morphine sulfate tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.
- Morphine sulfate tablets come in a child-resistant package.
- Keep morphine sulfate tablets and all medications out of the reach of children.

Do not take morphine sulfate tablets 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 tablets, 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 during pregnancy can cause withdrawal.
- **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 tablets with certain other medicines can cause serious side effects that could lead to death.

When taking morphine sulfate tablets:

- Do not change your dose. Take morphine sulfate tablets 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 tablets regularly, do not stop taking morphine sulfate without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused morphine sulfate tablets by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking morphine sulfate tablets DO NOT:

- Drive or operate heavy machinery, until you know how morphine sulfate affects you. Morphine sulfate tablets 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 tablets may cause you to overdose and die.

The possible side effects of morphine sulfate tablets:

- 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 tablets. 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
UPSHER-SMITH LABORATORIES, LLC
Maple Grove, MN 55369
For Medication Guides, please visit www.upsher-smith.com or call 1-888-650-3789.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised 1119

PRINCIPAL DISPLAY PANEL - 15 mg Tablet Bottle Label

NDC 0832-0273-11

CII

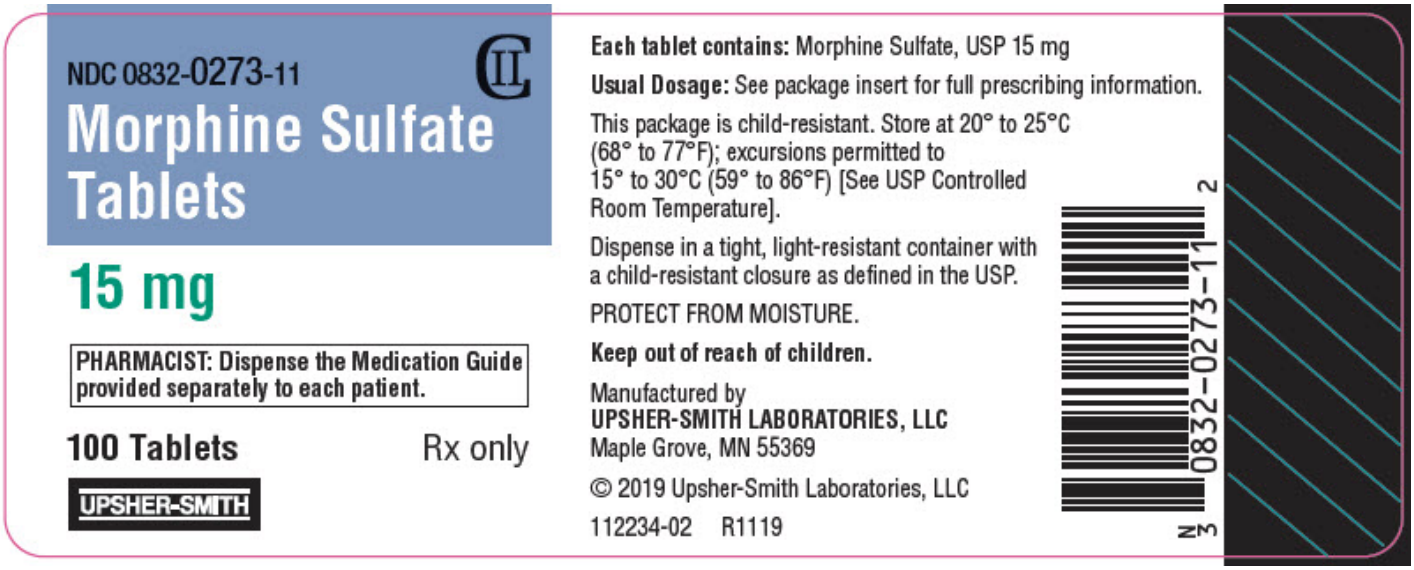
Morphine Sulfate
Tablets

15 mg

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

100 Tablets
Rx only

UPSHER-SMITH



PRINCIPAL DISPLAY PANEL - 30 mg Tablet Bottle Label

NDC 0832-0274-11

CII

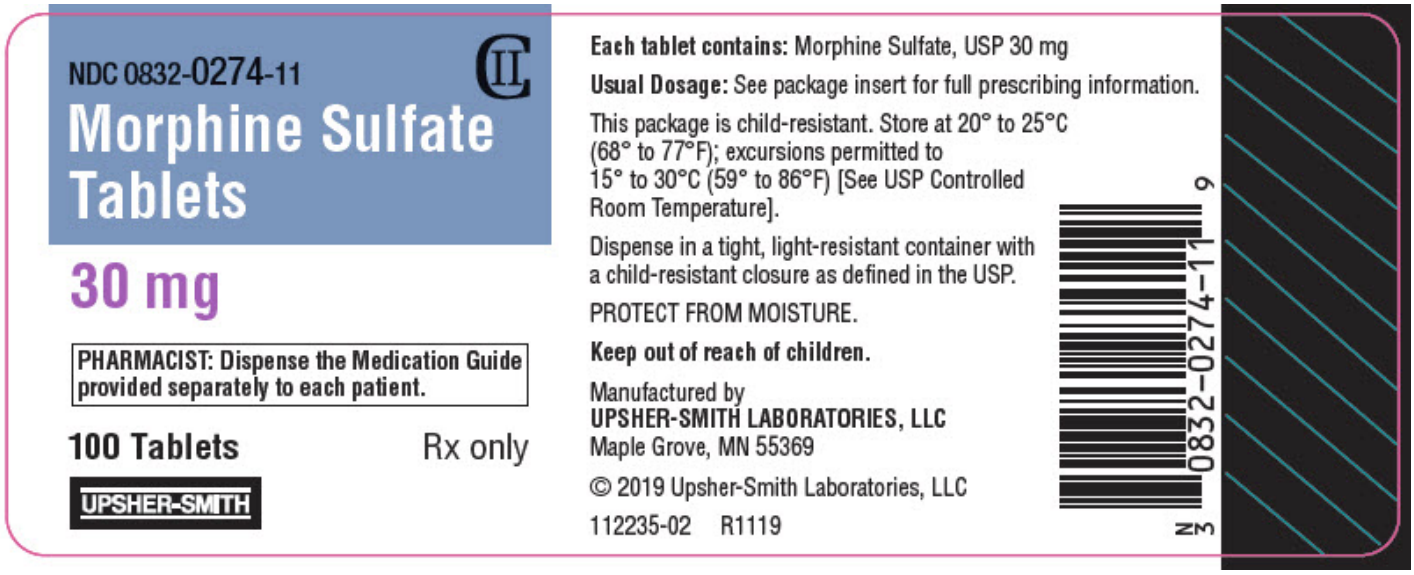
Morphine Sulfate
Tablets

30 mg

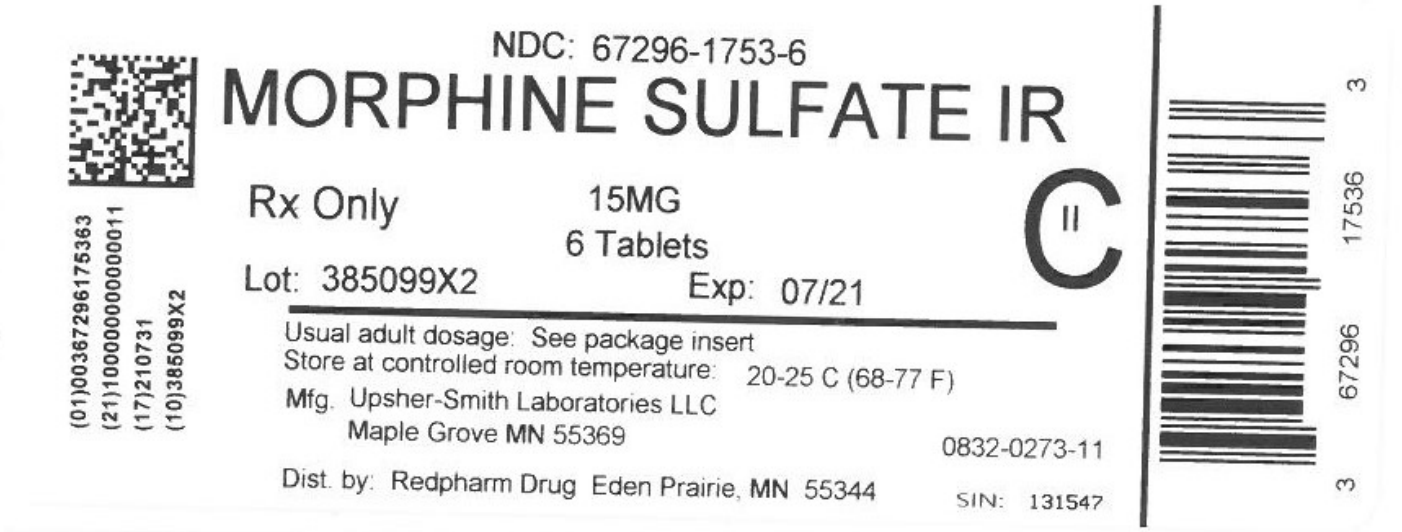
PHARMACIST: Dispense the Medication Guide provided separately to each patient.

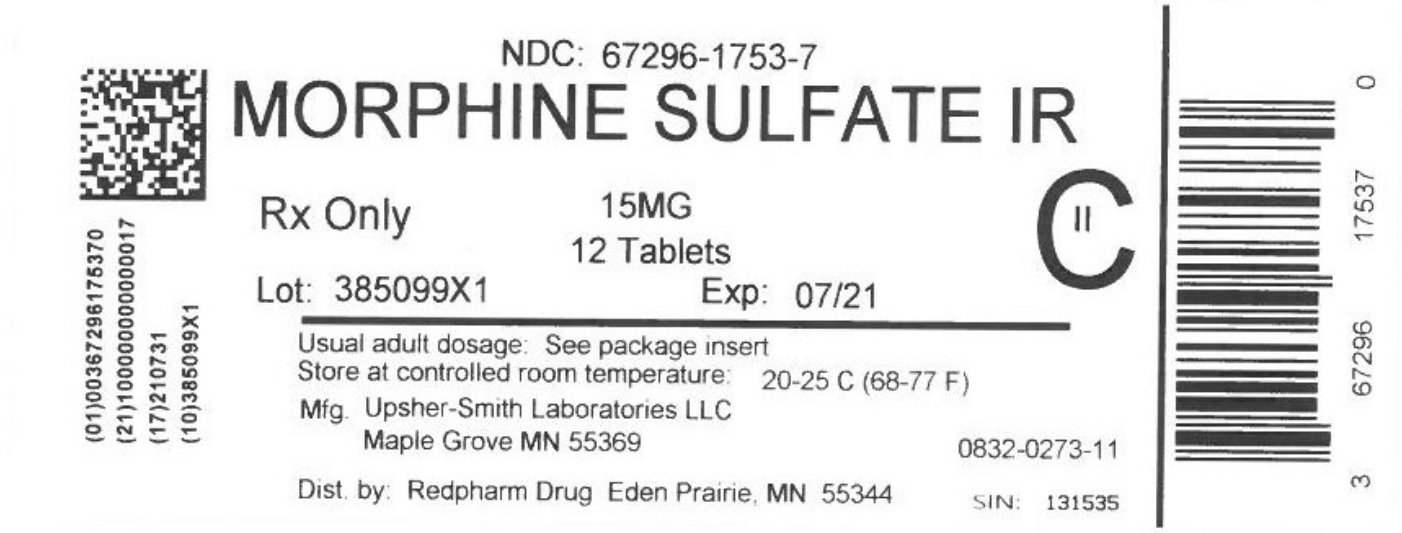
100 Tablets
Rx only

UPSHER-SMITH

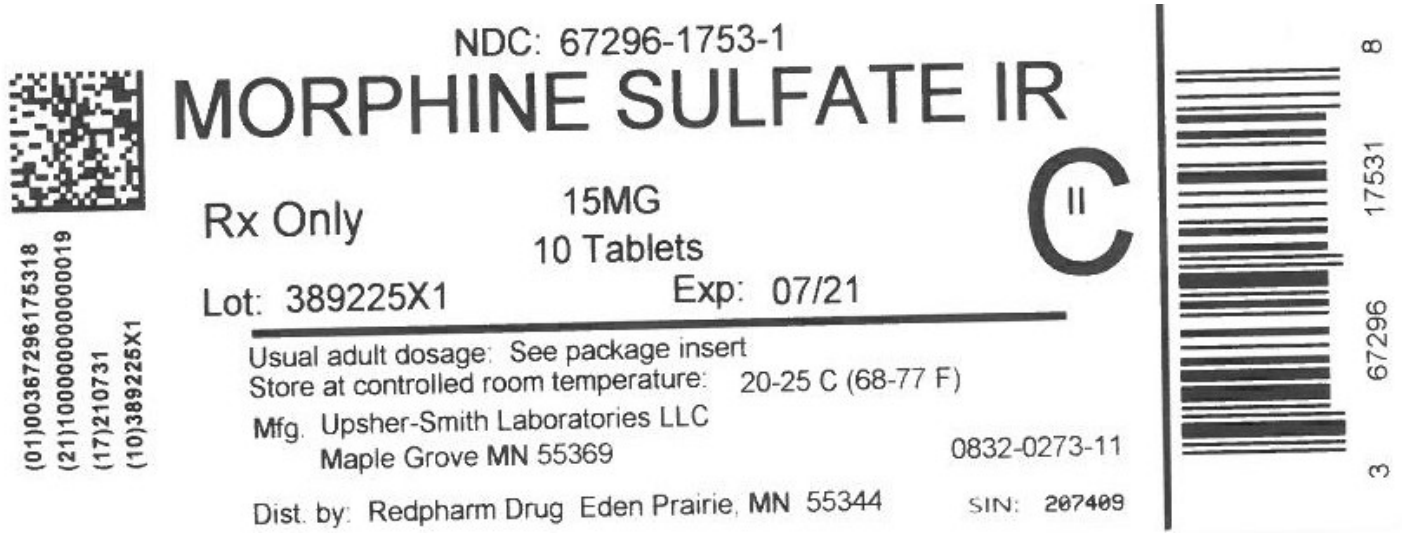


PACKAGE LABEL.PRINCIPAL DISPLAY PANEL





PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



MORPHINE SULFATE
morphine sulfate tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:67296-1753(NDC:0832-0273)
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MORPHINE SULFATE (UNII: X3P646A2J0) (MORPHINE - UNII:76I7G6D29C)	MORPHINE SULFATE	15 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	

Product Characteristics

Color	white	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	15;273
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67296-1753-6	6 in 1 BOTTLE; Type 0: Not a Combination Product	07/22/2019	
2	NDC:67296-1753-7	12 in 1 BOTTLE; Type 0: Not a Combination Product	07/22/2019	
3	NDC:67296-1753-1	10 in 1 BOTTLE; Type 0: Not a Combination Product	07/22/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210610	07/22/2019	

Labeler - RedPharm Drug, Inc. (828374897)

Establishment

Name	Address	ID/FEI	Business Operations

EPM Packaging		079124340	repack(67296-1753)