

MORPHINE SULFATE EXTENDED RELEASE- morphine sulfate tablet, film coated, extended release

Bryant Ranch Prepack

HIGHLIGHTS OF PRESCRIBING INFORMATION

Morphine Sulfate Extended-Release Tablets, CII

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

morphine sulfate (morphine sulfate) TABLET, FILM COATED, EXTENDED RELEASE for ORAL use.

Initial U.S. Approval: 1941

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

See full prescribing information for complete boxed warning.

- Morphine sulfate extended-release tablets contain morphine sulfate, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during morphine sulfate extended-release tablet therapy (5.1, 9).
- Fatal respiratory depression may occur, with highest risk at initiation and with dose increases. Instruct patients on proper administration of morphine sulfate extended-release tablets to reduce the risk (5.2).
- Accidental ingestion of morphine sulfate extended-release tablets can result in fatal overdose of morphine, especially in children (5.3).

RECENT MAJOR CHANGES

Boxed Warning	2/2012
Indications and Usage (1)	2/2012
Dosage and Administration (2)	2/2012
Contraindications (4)	2/2012
Warnings and Precautions (5)	2/2012

INDICATIONS AND USAGE

Morphine sulfate extended-release tablets are an opioid agonist product indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

Limitations of Use

- Morphine sulfate extended-release tablets are not for use:
 - As an as-needed (prn) analgesic (1)
 - For pain that is mild or not expected to persist for an extended period of time (1)
 - For acute pain (1)
 - In the immediate postoperative period (1)
 - For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1)
- Morphine sulfate extended-release 100 mg and 200 mg tablets are only for patients in whom tolerance to an opioid of comparable potency is established. (1)

DOSAGE AND ADMINISTRATION

- Individualize dosing based on patient's prior analgesic treatment experience, and titrate as needed to provide adequate analgesia and minimize adverse reactions. (2.1, 2.2)
- Do not abruptly discontinue morphine sulfate extended-release tablets in a physically dependent patient. (2.3)
- Instruct patients to swallow morphine sulfate extended-release tablets intact. (2.4)

DOSAGE FORMS AND STRENGTHS

Tablets (morphine sulfate): 15 mg, 30 mg, 60 mg, 100 mg, 200 mg (3)

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Hypersensitivity to morphine (4)

WARNINGS AND PRECAUTIONS

- Elderly, cachectic, and debilitated patients, and patients with chronic pulmonary disease: Monitor closely because of increased risk of respiratory depression. (5.4, 5.5)
- Interaction with CNS depressants: Consider dose reduction of one or both drugs because of additive effects. (5.6, 7.1)
- Hypotensive effect: Monitor during dose initiation and titration (5.7)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of morphine sulfate extended-release tablets in patients with impaired consciousness or coma susceptible to intracranial effects of CO₂ retention. (5.8)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions: constipation, nausea, and sedation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Rhodes Pharmaceuticals L.P. at 1-888-827-0616 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

- Mixed agonist/antagonist opioid analgesics: Avoid use with morphine sulfate extended-release tablets because they may reduce analgesic effect of morphine sulfate extended-release tablets or precipitate withdrawal symptoms. (5.11, 7.2)
- Muscle relaxants: Avoid use with morphine sulfate extended-release tablets because of increased risk of respiratory depression. (7.3)
- Monoamine oxidase inhibitors (MAOIs): Avoid morphine sulfate extended-release tablets in patients taking MAOIs or within 14 days of stopping such treatment. (7.4)

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

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: Morphine has been detected in human milk. Closely monitor infants of nursing women receiving morphine sulfate extended-release tablets. (8.3)

See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**.

Revised: 5/2012

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

Morphine sulfate extended-release tablets contain morphine; an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [see *Warnings and Precautions (5.1)*]. Assess each patient's risk for opioid abuse or addiction prior to prescribing morphine sulfate extended-release tablets. The risk for opioid abuse is 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 depressive disorder). Routinely monitor all patients receiving morphine sulfate extended-release tablets for signs of misuse, abuse, and addiction during treatment [see *Drug Abuse and Dependence (9)*].

Life-Threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of morphine sulfate extended-release tablets, even when the drug has been used as recommended and not misused or abused [see *Warnings and Precautions (5.2)*]. Proper dosing and titration are essential and morphine sulfate extended-release tablets should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of morphine sulfate extended-release tablets or following a dose increase. Instruct patients to swallow morphine sulfate extended-release tablets whole. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of morphine.

Accidental Exposure

Accidental ingestion of morphine sulfate extended-release tablets, especially in children, can result in a fatal overdose of morphine [see *Warnings and Precautions (5.3)*].

1 INDICATIONS & USAGE

Morphine Sulfate Extended-Release Tablets are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Use

Morphine sulfate extended-release tablets are not for use:

- As an as-needed (prn) analgesic.
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- In the immediate postoperative period (the first 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

Morphine sulfate extended-release 100 mg and 200 mg tablets are only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid-tolerant are those taking at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

2 DOSAGE & ADMINISTRATION

2.1 Initial Dosing

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with morphine sulfate extended-release tablets [see *Warnings and Precautions* (5.2)].

Consider the following factors when selecting an initial dose of morphine sulfate extended-release tablets:

- Total daily dose, potency, and any prior opioid the patient has been taking previously;
- Reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed (Note: potency estimates may vary with the route of administration);
- Patient's degree of opioid experience and opioid tolerance;
- General condition and medical status of the patient;
- Concurrent medication;
- Type and severity of the patient's pain.

Morphine sulfate extended-release tablets are administered at a frequency of twice daily (every 12 hours) or three times daily (every 8 hours).

Use of Morphine Sulfate Extended-Release Tablets as the First Opioid Analgesic

There has been no systematic evaluation of morphine sulfate extended-release tablets as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient using controlled-release morphine, it is ordinarily advisable to begin treatment using an immediate-release formulation.

Conversion from Other Oral Morphine to Morphine Sulfate Extended-Release Tablets

Patients receiving other oral morphine formulations may be converted to morphine sulfate extended-release tablets by administering one-half of the patient's 24-hour requirement as morphine sulfate extended-release tablets on an every-12-hour schedule or by administering one-third of the patient's daily requirement as morphine sulfate extended-release tablets on an every-8-hour schedule.

Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Extended-Release Tablets

While there are useful tables of oral and parenteral equivalents, there is substantial inter-patient variability in the relative potency of different opioid drugs and formulations. As such, it is safer to underestimate a patient's 24-hour oral morphine dose and provide rescue medication (e.g., immediate-release morphine) than to overestimate the 24-hour oral morphine dose and manage an adverse reaction. Consider the following general points:

Parenteral to oral morphine ratio: Between 2 to 6 mg of oral morphine may be required to provide analgesia equivalent to 1 mg of parenteral morphine. Typically, a dose of morphine that is approximately three times the previous daily parenteral morphine requirement is sufficient.

Other parenteral or oral non-morphine opioids to oral morphine sulfate: Specific recommendations are not available because of a lack of systematic evidence for these types of analgesic substitutions. Published relative potency data are available, but such ratios are approximations. In general, begin with half of the estimated daily morphine requirement as the initial dose, managing inadequate analgesia by supplementation with immediate-release morphine.

The first dose of morphine sulfate extended-release tablets may be taken with the last dose of any immediate-release opioid medication due to the extended-release characteristics of the morphine sulfate extended-release tablets formulation.

2.2 Titration and Maintenance of Therapy

Individually titrate morphine sulfate extended-release tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving morphine sulfate extended-release tablets to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), periodically reassess the continued need for the use of opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the morphine sulfate extended-release tablets dose to decrease the level of pain. Because steady-state plasma concentrations are approximated in 1 day, morphine sulfate extended-release tablets dosage adjustments may be done every 1 to 2 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid and non-opioid medication.

If signs of excessive opioid-related adverse reactions are observed, the next dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

During chronic, around-the-clock opioid therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

2.3 Discontinuation of Morphine Sulfate Extended-Release Tablets

When the patient no longer requires therapy with morphine sulfate extended-release tablets, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue morphine sulfate extended-release tablets.

2.4 Administration of Morphine Sulfate Extended-Release Tablets

Instruct patients to swallow morphine sulfate extended-release tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of morphine [see *Warnings and Precautions (5.2)*].

3 DOSAGE FORMS & STRENGTHS

- Morphine sulfate extended-release tablets 15 mg
Round, blue-colored, film-coated tablets bearing the symbol ABG on one side and 15 on the other
- Morphine sulfate extended-release tablets 30 mg
Round, lavender-colored, film-coated tablets bearing the symbol ABG on one side and 30 on the other
- Morphine sulfate extended-release tablets 60 mg
Round, orange-colored, film-coated tablets bearing the symbol ABG on one side and 60 on the other
- Morphine sulfate extended-release tablets 100 mg*
Round, gray-colored, film-coated tablets bearing the symbol ABG on one side and 100 on the other
- Morphine sulfate extended-release tablets 200 mg*
Capsule-shaped, green-colored, film-coated tablets bearing the symbol ABG on one side and 200 on the other

***100 mg and 200 mg tablets are for use in opioid-tolerant patients only**

4 CONTRAINDICATIONS

Morphine sulfate extended-release tablets are contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (e.g., anaphylaxis) to morphine [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

Morphine sulfate extended-release tablets contain morphine, an opioid agonist and a Schedule II controlled substance. Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists 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 extended-release tablets in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient's risk for opioid abuse or addiction prior to prescribing morphine sulfate extended-release tablets. The risk for opioid abuse is 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). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of morphine sulfate extended-release tablets by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death [*see Overdosage (10)*].

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

Respiratory depression is the chief hazard of opioid agonists, including morphine sulfate extended-release tablets. Respiratory depression if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. 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)*].

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of morphine sulfate extended-release tablets, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with morphine sulfate extended-release tablets and following dose increases. Instruct patients against use by individuals other than the patient for whom morphine sulfate extended-release tablets were prescribed and to keep morphine sulfate extended-release tablets out of the reach of children, as such inappropriate use may result in fatal respiratory depression.

To reduce the risk of respiratory depression, proper dosing and titration of morphine sulfate extended-release tablets are essential [*see Dosage and Administration (2)*]. Overestimating the morphine sulfate extended-release tablets dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-

release opioids when used as recommended and not misused or abused.

To further reduce the risk of respiratory depression, consider the following:

- Proper dosing and titration are essential and morphine sulfate extended-release tablets should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Morphine sulfate extended-release 100 mg and 200 mg tablets are for use in opioid-tolerant patients only. Ingestion of these strengths of morphine sulfate extended-release tablets may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.
- Instruct patients to swallow morphine sulfate extended-release tablets intact. The tablets are not to be crushed, dissolved, or chewed. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals.
- Morphine sulfate extended-release tablets are contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression [*see Contraindications (4)*].

5.3 Accidental Exposure

Accidental consumption of morphine sulfate extended-release tablets, especially in children, can result in a fatal overdose of morphine.

5.4 Elderly, Cachectic, and Debilitated Patients

Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Therefore, monitor such patients closely, particularly when initiating and titrating morphine sulfate extended-release tablets and when morphine sulfate extended-release tablets are given concomitantly with other drugs that depress respiration [*see Warnings and Precautions (5.2)*].

5.5 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with morphine sulfate extended-release tablets, as in these patients, even usual therapeutic doses of morphine sulfate extended-release tablets may decrease respiratory drive to the point of apnea [*see Warnings and Precautions (5.2)*]. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.6 Interactions with Alcohol, CNS Depressants, and Illicit Drugs

Hypotension, and profound sedation, coma or respiratory depression may result if morphine sulfate extended-release tablets are used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, muscle relaxants, other opioids). When considering the use of morphine sulfate extended-release tablets in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, consider the patient's use, if any, of alcohol and/or illicit drugs that can cause CNS depression. If morphine sulfate extended-release tablet therapy is to be initiated in a patient taking a CNS depressant, start with a lower morphine sulfate extended-release tablet dose than usual and monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant [*see Drug Interactions (7.1)*].

5.7 Hypotensive Effects

Morphine sulfate extended-release tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an 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 (7.1)*]. Monitor these patients for signs of hypotension after initiating or titrating the dose of morphine sulfate extended-release tablets. In patients with circulatory shock, morphine sulfate extended-release tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of morphine sulfate extended-release tablets in patients with circulatory shock.

5.8 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking morphine sulfate extended-release tablets that may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with morphine sulfate extended-release tablets. Morphine sulfate extended-release tablets may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of morphine sulfate extended-release tablets in patients with impaired consciousness or coma.

5.9 Use in Patients with Gastrointestinal Conditions

Morphine sulfate extended-release tablets are contraindicated in patients with paralytic ileus. Avoid the use of morphine sulfate extended-release tablets in patients with other GI obstruction.

The morphine in morphine sulfate extended-release tablets may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms. Opioids may cause increases in the serum amylase.

5.10 Use in Patients with Convulsive or Seizure Disorders

The morphine in morphine sulfate extended-release tablets may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during morphine sulfate extended-release tablet therapy.

5.11 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including morphine sulfate extended-release tablets. In these patients, mixed agonists/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing morphine sulfate extended-release tablets, gradually taper the dose [*see Dosage and Administration (2.3)*]. Do not abruptly discontinue morphine sulfate extended-release tablets.

5.12 Driving and Operating Machinery

Morphine sulfate extended-release 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 extended-release tablets and know how they will react to the medication.

6 ADVERSE REACTIONS

The following adverse reactions described elsewhere in the labeling include:

- Respiratory Depression [*see Warnings and Precautions (5.2)*]
- Chronic Pulmonary Disease [*see Warnings and Precautions (5.5)*]
- Head Injuries and Increased Intracranial Pressure [*see Warnings and Precautions (5.8)*]
- Interactions with Other CNS Depressants [*see Warnings and Precautions (5.6)*]

- Hypotensive Effect [see Warnings and Precautions (5.7)]
- Gastrointestinal Effects [see Warnings and Precautions (5.9)]
- Seizures [see Warnings and Precautions (5.10)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Morphine sulfate extended-release tablets may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock [see Overdosage (10)].

Most Frequently Observed Reactions

In clinical trials, the most common adverse reactions with morphine sulfate extended-release tablets were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoric mood.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain.

Less Frequently Observed Reactions

Cardiovascular disorders: tachycardia, bradycardia, palpitations

Eye disorders: visual impairment, vision blurred, diplopia, miosis

Gastrointestinal disorders: dry mouth, diarrhea, abdominal pain, constipation, dyspepsia

General disorders and administration site conditions: chills, feeling abnormal, edema, edema peripheral, weakness

Hepatobiliary disorders: biliary colic

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: muscle rigidity, muscle twitching

Nervous system disorders: presyncope, syncope, headache, tremor, uncoordinated muscle movements, convulsion, intracranial pressure increased, taste alteration, paresthesia, nystagmus

Psychiatric disorders: agitation, mood altered, anxiety, depression, abnormal dreams, hallucination, disorientation, insomnia

Renal and urinary disorders: urinary retention, urinary hesitation, antidiuretic effects

Reproductive system and breast disorders: reduced libido and/or potency

Respiratory, thoracic and mediastinal disorders: laryngospasm

Skin and subcutaneous tissue disorders: pruritus, urticaria, rash

Vascular disorders: flushing, hypotension, hypertension

6.2 Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of morphine sulfate extended-release tablets: amenorrhea, asthenia, bronchospasm, confusional state, drug hypersensitivity, fatigue, hyperalgesia, hypertonia, ileus, increased hepatic enzymes, intestinal obstruction, lethargy, malaise, pulmonary edema, thinking disturbances, somnolence, and vertigo.

Anaphylaxis has been reported with ingredients contained in morphine sulfate extended-release tablets. Advise patients how to recognize such a reaction and when to seek medical attention.

7 DRUG INTERACTIONS

7.1 CNS Depressants

Concurrent use of morphine sulfate extended-release tablets and other central nervous system (CNS) depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol can increase the risk of respiratory depression, hypotension, profound sedation or coma. Monitor patients receiving CNS depressants and morphine sulfate extended-release tablets for signs of respiratory depression and hypotension. When such combined therapy is contemplated, reduce the initial dose of one or both agents.

7.2 Mixed Agonists/Antagonist Opioid Analgesics

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol) may reduce the analgesic effect of morphine sulfate extended-release tablets or may precipitate withdrawal symptoms in these patients. Avoid the use of agonist/antagonist analgesics in patients receiving morphine sulfate extended-release tablets.

7.3 Muscle Relaxants

Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and morphine sulfate extended-release tablets for signs of respiratory depression that may be greater than otherwise expected.

7.4 Monoamine Oxidase Inhibitors (MAOIs)

The effects of morphine may be potentiated by MAOIs. Monitor patients on concurrent therapy with an MAOI and morphine sulfate extended-release tablets for increased respiratory and central nervous system depression. MAOIs have been reported to potentiate the effects of morphine anxiety, confusion, and significant depression of respiration or coma. Morphine sulfate extended-release tablets should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

7.5 Cimetidine

Cimetidine can potentiate morphine-induced respiratory depression. There is a report of confusion and severe respiratory depression when a patient undergoing hemodialysis was concurrently administered morphine and cimetidine. Monitor patients for respiratory depression when morphine sulfate extended-release tablets and cimetidine are used concurrently.

7.6 Diuretics

Morphine can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with enlarged prostates.

7.7 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when morphine sulfate extended-release tablets are used concurrently with anticholinergic drugs.

7.8 P-Glycoprotein (PGP) Inhibitors

PGP-inhibitors (e.g., quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold. Therefore, monitor patients for signs of respiratory and central nervous system depression when morphine sulfate extended-release tablets are used concurrently with PGP inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects (Pregnancy Category C)

No formal studies to assess the teratogenic effects of morphine in animals have been conducted. It is also not known whether morphine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Morphine should be given to a pregnant woman only if clearly needed.

In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternbrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed. No maternal toxicity was observed in this study; however, increased mortality and growth retardation were seen in the offspring. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.

Non-Teratogenic Effects

Infants born to mothers who have taken opioids chronically may exhibit neonatal withdrawal syndrome [see *Use in Specific Populations (8.6)*], reversible reduction in brain volume, small size, decreased ventilatory response to CO₂ and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Published literature has reported that exposure to morphine during pregnancy in animals is associated with reduction in growth and a host of behavioral abnormalities in the offspring. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. Decreased fertility in female offspring, 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. Decreased litter size and viability were observed in the offspring of male rats administered morphine (25 mg/kg, IP) for 1 day prior to mating. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine persisting into adulthood.

8.2 Labor & Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Morphine sulfate extended-release tablets are not recommended for use in women during and immediately prior to labor. Occasionally, opioid analgesics may 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 dilatation which tends to shorten labor.

Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. An opioid antagonist, naloxone, should be available for reversal of opioid-induced respiratory depression in the neonate in such situations.

8.3 Nursing Mothers

Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. The amount of morphine received by the infant varies depending on the maternal plasma concentration, the amount of milk ingested by the infant, and the extent of first pass metabolism.

Withdrawal signs can occur in breast-feeding infants when maternal administration of morphine is stopped.

Because of the potential for adverse reactions in nursing infants from morphine sulfate extended-release tablets, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

The pharmacokinetics of morphine sulfate extended-release tablets has not been studied in elderly patients. Clinical studies of morphine sulfate extended-release tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, 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.

8.6 Neonatal Opioid Withdrawal Syndrome

Chronic maternal use of morphine during pregnancy can affect the fetus with subsequent withdrawal signs. Neonatal 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 drug used, duration of use, the dose of last maternal use, and rate of elimination of the drug by the newborn. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Morphine sulfate extended-release tablets contain morphine, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. Morphine sulfate extended-release tablets can be abused and are subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions (5.1)*].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use

of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: 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 to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(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. Physicians 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 extended-release tablets, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests as required by state law, is strongly advised.

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

Risks Specific to Abuse of Morphine Sulfate Extended-Release Tablets

Morphine sulfate extended-release tablets are for oral use only. Abuse of morphine sulfate extended-release tablets poses a risk of overdose and death. This risk is increased with concurrent abuse of morphine sulfate extended-release tablets with alcohol and other substances. Taking cut, broken, chewed, crushed, or morphine sulfate extended-release tablets enhance drug release and increases the risk of overdose and death.

Due to the presence of talc as one of the excipients in morphine sulfate extended-release tablets, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. 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 dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Morphine sulfate extended-release tablets should not be abruptly discontinued [*see Dosage and*

Administration (2.3)]. If morphine sulfate extended-release tablets are abruptly discontinued in a physically-dependent patient, an abstinence 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 (8.6)*].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with morphine is 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, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

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, 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. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Such agents should be administered cautiously to persons who are known, or suspected to be physically dependent on morphine sulfate extended-release tablets. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Because the duration of reversal would be expected to be less than the duration of action of morphine in morphine sulfate extended-release tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. Morphine sulfate extended-release tablets will continue to release morphine and add to the morphine load for 24 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be administered as directed in the product's prescribing information.

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

11 DESCRIPTION

Morphine Sulfate Extended-Release Tablets are for oral use and contain morphine sulfate, an agonist at the mu-opioid receptor.

Each tablet contains the following inactive ingredients common to all strengths: cetostearyl alcohol, hydroxyethyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, talc and titanium dioxide.

The tablet strengths describe the amount of morphine per tablet as the pentahydrated sulfate salt (morphine sulfate).

The 15 mg tablets also contain: FD&C Blue No. 2, lactose monohydrate, polysorbate 80

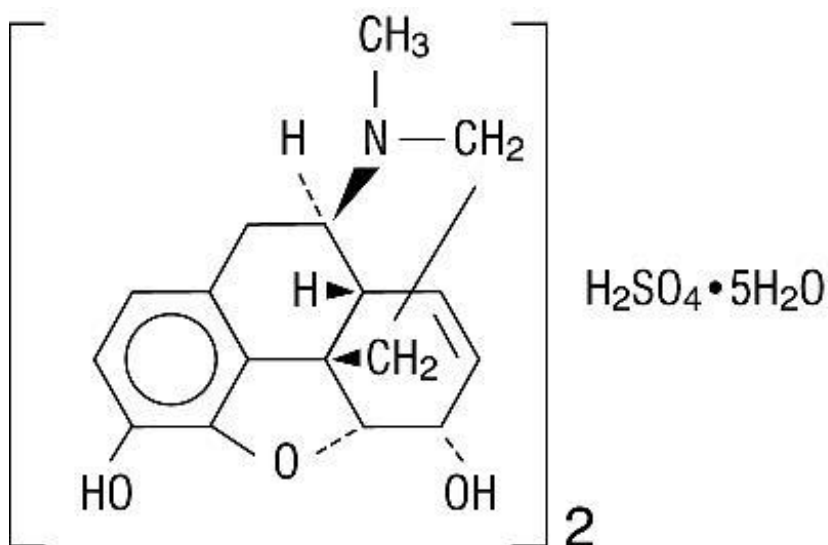
The 30 mg tablets also contain: D&C Red No. 7, FD&C Blue No. 1, lactose monohydrate, polysorbate 80

The 60 mg tablets also contain: D&C Red No. 30, D&C Yellow No. 10, hydroxypropyl cellulose, lactose monohydrate

The 100 mg tablets also contain: black iron oxide

The 200 mg tablets also contain: D&C Yellow No. 10, FD&C Blue No. 1, hydroxypropyl cellulose

Morphine sulfate is an odorless, white, crystalline powder with a bitter taste. It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol: water partition coefficient of morphine is 1.42 at physiologic pH and the pK_b is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4). Its structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Morphine sulfate, an opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine sulfate include analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release, physical dependence, and alterations of the endocrine and autonomic nervous systems.

Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors located throughout the body. Morphine acts as a full agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

Effects on the Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation. Specific CNS opiate receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects.

Morphine produces respiratory depression by direct action on brainstem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brainstem

respiratory centers to increases in carbon dioxide tension, and to electrical stimulation.

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic 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 with worsening hypoxia.

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 in the duodenum. Digestion of food is delayed in the small intestine and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm. The end result is constipation. Morphine can cause a marked reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

Effects on the Endocrine System

Opioids inhibit the secretion of ACTH, cortisol, testosterone, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

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.

12.2 Pharmacodynamics

Plasma Level-Analgesia Relationships

While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when morphine sulfate extended-release tablets are used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

12.3 Pharmacokinetics

Morphine sulfate extended-release tablets are a controlled-release tablet containing morphine sulfate. Morphine is released from morphine sulfate extended-release tablets somewhat more slowly than from immediate-release oral preparations. Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same whether the source is morphine sulfate extended-release tablets or an immediate-release formulation. Because of pre-systemic elimination (i.e., metabolism in the gut wall and liver) only about 40% of the administered dose reaches the central compartment.

Absorption

The oral bioavailability of morphine is approximately 20 to 40%. When morphine sulfate extended-

release tablets are given on a fixed dosing regimen, steady-state is achieved in about a day.

Food Effect

The effect of food upon the systemic bioavailability of morphine sulfate extended-release tablets has not been systematically evaluated for all strengths. One study, conducted with the 30 mg morphine sulfate extended-release tablets, showed no significant differences in C_{max} and AUC (0-24h) values, whether the tablet was taken while fasting or with a high-fat breakfast.

Distribution

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. Morphine also crosses placental membranes and has been found in breast milk. The volume of distribution (Vd) for morphine is approximately 3 to 4 liters per kilogram and morphine is 30 to 35% reversibly bound to plasma proteins.

Metabolism

The major pathways of morphine metabolism include glucuronidation to produce metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5 to 15%) and sulfation in the liver to produce morphine-3-etheral sulfate. A small fraction (less than 5%) of morphine is demethylated. M6G has been shown to have analgesic activity but crosses the blood-brain barrier poorly, while M3G has no significant analgesic activity.

Excretion

The elimination of morphine occurs primarily as renal excretion of M3G and its effective half-life after intravenous administration is normally 2 to 4 hours. Approximately 10% of the dose is excreted unchanged in urine. In some studies involving longer periods of plasma sampling, a longer terminal half-life of about 15 hours was reported. A small amount of the glucuronide conjugate is excreted in the bile, and there is some minor enterohepatic recycling.

Special Populations

Geriatric Patients

The pharmacokinetics of morphine sulfate extended-release tablets have not been studied in elderly patients.

Pediatric Patients

The pharmacokinetics of morphine sulfate extended-release tablets has not been studied in pediatric patients below the age of 18.

Gender

A gender analysis of pharmacokinetic data from healthy subjects taking morphine sulfate extended-release tablets indicated that morphine concentrations were similar in males and females.

Race

Chinese subjects given intravenous morphine had a higher clearance when compared to Caucasian subjects (1852 +/- 116 mL/min compared to 1495 +/- 80 mL/min).

Hepatic Impairment

Morphine pharmacokinetics are altered in individuals with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma 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: 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, higher incidence of pseudopregnancies, and reduction in implantation sites were seen. Studies from the literature have also reported changes in hormonal levels (i.e., testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.

16 HOW SUPPLIED/STORAGE AND HANDLING

Morphine Sulfate Extended-Release Tablets 15 mg are round, blue-colored, film-coated tablets bearing the symbol ABG on one side and 15 on the other. They are supplied as follows:

NDC 42858-801-01: opaque plastic bottles containing 100 tablets

Morphine Sulfate Extended-Release Tablets 30 mg are round, lavender-colored, film-coated tablets bearing the symbol ABG on one side and 30 on the other. They are supplied as follows:

NDC 42858-802-01: opaque plastic bottles containing 100 tablets

Morphine Sulfate Extended-Release Tablets 60 mg are round, orange-colored, film-coated tablets bearing the symbol ABG on one side and 60 on the other. They are supplied as follows:

NDC 42858-803-01: opaque plastic bottles containing 100 tablets

Morphine Sulfate Extended-Release Tablets 100 mg are round, gray-colored, film-coated tablets bearing the symbol ABG on one side and 100 on the other. They are supplied as follows:

NDC 42858-804-01: opaque plastic bottles containing 100 tablets

Morphine Sulfate Extended-Release Tablets 200 mg are capsule-shaped, green-colored, film-coated tablets bearing the symbol ABG on one side and 200 on the other. They are supplied as follows:

NDC 42858-805-01: opaque plastic bottles containing 100 tablets

Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F).

Dispense in a tight, light-resistant container.

CAUTION

DEA FORM REQUIRED

17 INFORMATION FOR PATIENTS

See FDA-approved patient labeling (Medication Guide)

Abuse Potential

Inform patients that morphine sulfate extended-release tablets contain morphine, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share morphine sulfate extended-release tablets with others and to take steps to protect morphine sulfate extended-release tablets from theft or misuse.

Life-Threatening Respiratory Depression

Discuss the risk of respiratory depression with patients, explaining that the risk is greatest when starting morphine sulfate extended-release tablets or when the dose is increased. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Exposure

Instruct patients to take steps to store morphine sulfate extended-release tablets securely. Accidental exposure, especially in children, may result in serious harm or death. Advise patients to dispose of unused morphine sulfate extended-release tablets by flushing the tablets down the toilet.

Risks from Concomitant Use of Alcohol and other CNS Depressants

Inform patients that the concomitant use of alcohol with morphine sulfate extended-release tablets can increase the risk of life-threatening respiratory depression. Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter drug products that contain alcohol, during treatment with morphine sulfate extended-release tablets.

Inform patients that potentially serious additive effects may occur if morphine sulfate extended-release tablets are used with other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Important Administration Instructions

Instruct patients how to properly take morphine sulfate extended-release tablets, including the following:

- Swallowing morphine sulfate extended-release tablets whole
- Not crushing, chewing, or dissolving the tablets
- Using morphine sulfate extended-release tablets exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Not discontinuing morphine sulfate extended-release tablets without first discussing the need for a tapering regimen with the prescriber

Hypotension

Inform patients that morphine sulfate extended-release 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).

Driving or Operating Heavy Machinery

Inform patients that morphine sulfate extended-release 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.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in morphine sulfate extended-release tablets. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Advise female patients that morphine sulfate extended-release tablets can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Healthcare professionals can telephone Rhodes Pharmaceuticals L.P. (1-888-827-0616) for information on this product.

Marketed by:

Rhodes Pharmaceuticals L.P.
Coventry, RI 02816

Manufactured by:

Purdue Pharmaceuticals, L.P.
Wilson, NC 27893

302567-0A

Rev. 05/12

MEDICATION GUIDE

Morphine Sulfate Extended-Release (ER) Tablets, CII

Morphine sulfate extended-release tablets are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to treat moderate to severe around-the-clock pain.

Important information about morphine sulfate extended-release tablets:

- Get emergency help right away if you take too much morphine sulfate ER tablets (overdose). Morphine sulfate ER overdose can cause life threatening breathing problems that can lead to death.
- Never give anyone else your morphine sulfate extended-release tablets. They could die from taking it. Store morphine sulfate ER tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away morphine sulfate extended-release tablets is against the law.

Do not take morphine sulfate extended-release tablets if you have:

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

Before taking morphine sulfate ER, 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. Morphine sulfate may harm your unborn baby.
- breastfeeding. Morphine sulfate passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements.

When taking morphine sulfate extended-release tablets:

- Do not change your dose. Take morphine sulfate extended-release tablets exactly as prescribed by your healthcare provider.
- Take each dose at the same time every day. If you miss a dose, take morphine sulfate extended-release tablets as soon as possible and then take your next dose 8 or 12 hours later as directed by your healthcare provider. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take more than 1 dose in 8 hours.
- Swallow morphine sulfate extended-release tablets whole. Do not cut, break, chew, crush, dissolve, or inject morphine sulfate extended-release tablets.
- Call your healthcare provider if the dose you are taking does not control your pain.
- Do not stop taking morphine sulfate ER without talking to your healthcare provider.
- After you stop taking morphine sulfate ER tablets, flush any unused tablets down the toilet.

While taking morphine sulfate extended-release tablets Do Not:

- Drive or operate heavy machinery, until you know how morphine sulfate extended-release tablets affect you. Morphine sulfate extended-release tablets can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

The possible side effects of morphine sulfate extended-release tablets are:

- 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, or you are feeling faint.

These are not all the possible side effects of morphine sulfate extended-release 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 for: Rhodes Pharmaceuticals L.P., or call 1-888-827-0616

302828-0A

This Medication Guide has been approved by the U.S. FDA

Issue: 07/2012

Morphine Sulfate ER 60mg (CII) Tab.

<i>Packaged by Bryant Ranch</i>		<i>North Hollywood, CA 91605</i>	
Morphine Sulfate		LOT	ORANGE ROUND 60 ABG
ER 60mg (CII)		53145	
Tab.			
Compare To:			
Morphine Sulfate ER 60mg (CII) Tab.			
Purdue Pharmaceuticals L.P.			
# 100	Exp: MM/YY	FX ONLY	
NDC	6362945156		
			May Cause Drowsiness/No Alcohol
			Store at room temp of 20-25 C (68-77F)
			
			04515153145

MORPHINE SULFATE EXTENDED RELEASE

morphine sulfate tablet, film coated, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:63629- 4515(NDC:42858-803)
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	60 mg

Inactive Ingredients

Ingredient Name	Strength
CETOSTEARYL ALCOHOL (UNII: 2DMT128M1S)	
HYDROXYETHYL CELLULOSE (140 MPAS AT 5%) (UNII: 8136Y38GY5)	
HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
LACTOSE (UNII: J2B2A4N98G)	
D&C RED NO. 30 (UNII: 2S42T2808B)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	ORANGE	Score	no score
Shape	ROUND	Size	7mm
Flavor		Imprint Code	ABG;60
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-4515-1	30 in 1 BOTTLE		
2	NDC:63629-4515-2	60 in 1 BOTTLE		
3	NDC:63629-4515-3	90 in 1 BOTTLE		
4	NDC:63629-4515-4	120 in 1 BOTTLE		
5	NDC:63629-4515-5	5 in 1 BOTTLE		
6	NDC:63629-4515-6	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074862	01/14/2011	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-4515) , RELABEL(63629-4515)

Revised: 10/2012

Bryant Ranch Prepack