HIGHLIGHTS OF PRESCRIBING INFORMATION

Morphine Sulfate Extended-Release Capsules, USP for oral use, CII
These highlights do not include all the information needed to use morphine sulfate extended-release capsules safely and effectively. See full prescribing information for morphine sulfate extended-release capsules.

Morphine Sulfate Extended-Release Capsules, for oral use
Initial U.S. Approval: 1941

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL
See full prescribing information for complete boxed warning.

- **Morphine sulfate extended-release capsules exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow morphine sulfate extended-release capsules whole to avoid exposure to a potentially fatal dose of morphine. (5.2)**
- **Accidental ingestion of morphine sulfate extended-release capsules, especially in children, can result in fatal overdose of morphine. (5.3)**
- **Prolonged use of morphine sulfate extended-release capsules during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. 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. (5.3)**
- **Instruct patients not to consume alcohol or any products containing alcohol while taking morphine sulfate extended-release capsules because co-ingestion can result in fatal plasma morphine levels. (5.4)**

RECENT MAJOR CHANGES

Boxed Warning	04/2014
Indications and Usage (1)	04/2014
Dosage and Administration (2)	04/2014
Warnings and Precautions (5)	04/2014

INDICATIONS AND USAGE

Morphine sulfate extended-release capsules is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve morphine sulfate extended-release capsules for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Morphine sulfate extended-release capsules is not indicated as an as-needed (prn) analgesic.

DOSAGE AND ADMINISTRATION

- Morphine sulfate extended-release capsules 100 mg capsules are only for patients in whom tolerance to an opioid of comparable potency has been established. Patients considered opioid-tolerant are those taking, for one week or longer, 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. (2.1)
- For opioid-naïve patients, initiate treatment using an immediate-release morphine formulation and then convert patients to morphine sulfate extended-release capsules. For opioid non-tolerant patients, initiate with a 30 mg capsule orally every 24 hours. (2.1)
- To convert to morphine sulfate extended-release capsules from another opioid, use available conversion factors to obtain estimated dose. (2.1)
- Do not abruptly discontinue morphine sulfate extended-release capsules in a physically dependent patient. (2.3, 5.11)
- Instruct patients to swallow morphine sulfate extended-release capsules intact, or to sprinkle the capsule contents on applesauce and immediately swallow. (2.4)

DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 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

- Interaction with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs because of additive pharmacological effects. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life threatening respiratory depression. (5.5, 5.6)
- Hypotensive effect: Monitor during dose initiation and titration (5.7)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression and avoid use of morphine sulfate extended-release capsules in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.8)

ADVERSE REACTIONS

Most common adverse reactions (>10%): constipation, nausea, and somnolence. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical, Inc. at 1-800-828-9393 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 capsules because they may reduce analgesic effect of morphine sulfate extended-release capsules or precipitate withdrawal symptoms. (5.11, 7.3)
- Monoamine oxidase inhibitors (MAOIs): Avoid morphine sulfate extended-release capsules in patients taking MAOIs or within 14 days of stopping such treatment. (7.5)

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 capsules. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL

Addiction, Abuse, and Misuse
Morphine sulfate extended-release capsules exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing morphine sulfate extended-release capsules, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of morphine sulfate extended-release capsules. Monitor for respiratory depression, especially during initiation of morphine sulfate extended-release capsules or following a dose increase. Instruct patients to swallow morphine sulfate extended-release capsules whole; crushing, chewing, or dissolving morphine sulfate extended-release capsules can cause rapid release and absorption of a potentially fatal dose of morphine *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion
Accidental ingestion of even one dose of morphine sulfate extended-release capsules, especially by children, can result in a fatal overdose of morphine *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of morphine sulfate extended-release capsules during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Interaction with Alcohol
Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking morphine sulfate extended-release capsules. The co-ingestion of alcohol with morphine sulfate extended-release capsules may result in increased plasma levels and a potentially fatal overdose of morphine *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE

Morphine sulfate extended-release capsules is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve morphine sulfate extended-release capsules for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Morphine sulfate extended-release capsules is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

Morphine sulfate extended-release capsules should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

Morphine sulfate extended-release capsules 100 mg capsules are only for patients in whom tolerance to an opioid of comparable potency has been established. Patients considered opioid-tolerant are those taking, for one week or longer, 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.

Initiate the dosing regimen for each patient individually, taking into account the patient's 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 with morphine sulfate extended-release capsules *[see Warnings and Precautions (5.2)]*.

Morphine sulfate extended-release capsules must be taken whole. Crushing, chewing, or dissolving the pellets in morphine sulfate extended-release capsules will result in uncontrolled delivery of morphine and can lead to overdose or death *[see Warnings and Precautions (5.2)]*. Patients who are unable to swallow morphine sulfate extended-release capsules should be instructed to sprinkle the capsule contents on applesauce and immediately swallow without chewing *[see Administration of morphine sulfate extended-release capsules (2.4)]*.

Morphine sulfate extended-release capsules is administered at a frequency of either once daily (every 24 hours) or twice daily (every 12 hours).

Use of Morphine Sulfate Extended-Release Capsules as the First Opioid Analgesic
There has been no evaluation of morphine sulfate extended-release capsules as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient to adequate analgesia using an extended-release morphine, begin treatment using an immediate-release morphine formulation and then convert patients to morphine sulfate extended-release capsules as described below.

Use of Morphine Sulfate Extended-Release Capsules in Patients who are not Opioid Tolerant
The starting dose for patients who are not opioid tolerant is morphine sulfate extended-release capsules 30 mg orally every 24 hours. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Conversion from Other Opioids to Morphine Sulfate Extended-Release Capsules
There are no established conversion ratios from other opioids to morphine sulfate extended-release capsules defined by clinical trials. Discontinue all other around-the-clock opioid drugs when morphine sulfate extended-release capsules therapy is initiated and initiate dosing using morphine sulfate extended-release capsules 30 mg orally every 24 hours.

While there are useful tables of opioid equivalents readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products. As such, it is safer to underestimate a patient's 24-hour oral morphine requirements and provide rescue medication (e.g. immediate-release morphine) than to overestimate the 24-hour oral morphine requirements which could result in an adverse reaction.

Conversion from Other Oral Morphine Formulations to Morphine Sulfate Extended-Release Capsules
Patients receiving other oral morphine formulations may be converted to morphine sulfate extended-release capsules by administering one-half of the patient's total daily oral morphine dose as morphine sulfate extended-release capsules twice daily or by administering the total daily oral morphine dose as morphine sulfate extended-release capsules once daily. There are no data to support the efficacy or safety of prescribing morphine sulfate extended-release capsules more frequently than every 12 hours.

Morphine sulfate extended-release capsules is not bioequivalent to other extended-release morphine preparations. Conversion from the same total daily dose of another extended-release morphine product to morphine sulfate extended-release capsules may lead to either excessive sedation at peak or inadequate analgesia at trough. Therefore, monitor patients closely when initiating morphine sulfate extended-release capsules therapy and adjust the dosage of morphine sulfate extended-release capsules as needed.

Conversion from Parenteral Morphine, or Other Opioids to Morphine Sulfate Extended-Release Capsules
When converting from parenteral morphine or other non-morphine opioids (parenteral or oral) to morphine sulfate extended-release capsules, consider the following general points:

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

Other Oral or Parenteral Opioids to Oral morphine sulfate extended-release capsules: 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.

Conversion from Methadone to Morphine Sulfate Extended-Release Capsules
Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

2.2 Titration and Maintenance of Therapy

Individually titrate morphine sulfate extended-release capsules to a dose that provides adequate analgesia and minimizes adverse reactions at a frequency of either once or twice daily. Continually reevaluate patients receiving morphine sulfate extended-release capsules 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. 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. During chronic therapy, 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 capsules dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within 24 to 36 hours, morphine sulfate extended-release capsules dosage adjustments may be done every 1 to 2 days.

Patients who experience breakthrough pain may require a dose increase of morphine sulfate extended-release capsules, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the morphine sulfate extended-release capsules dose. In patients experiencing inadequate analgesia with once daily dosing of morphine sulfate extended-release capsules, consider a twice daily regimen.

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

2.3 Discontinuation of Morphine Sulfate Extended-Release Capsules

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

2.4 Administration of Morphine Sulfate Extended-Release Capsules

Morphine sulfate extended-release capsules must be taken whole. Crushing, chewing, or dissolving the pellets in morphine sulfate extended-release capsules will result in uncontrolled delivery of morphine and can lead to overdose or death *[see Warnings and Precautions (5.2)]*.

Alternatively, the contents of the morphine sulfate extended-release capsules (pellets) may be sprinkled over applesauce and then swallowed. This method is appropriate only for patients able to reliably swallow the applesauce without chewing. Other foods have not been tested and should not be substituted for applesauce. Instruct the patient to:

- Sprinkle the pellets onto a small amount of applesauce and consume immediately without chewing.
- Rinse the mouth to ensure all pellets have been swallowed.
- Discard any unused portion of the morphine sulfate extended-release capsules after the contents have been sprinkled on applesauce.

The contents of the morphine sulfate extended-release capsules (pellets) may be administered through a 16 French gastrostomy tube.

1. Flush the gastrostomy tube with water to ensure that it is wet.
2. Sprinkle the morphine sulfate extended-release capsules Pellets into 10 mL of water.
3. Use a swirling motion to pour the pellets and water into the gastrostomy tube through a funnel.
4. Rinse the beaker with a further 10 mL of water and pour this into the funnel.
5. Repeat rinsing until no pellets remain in the beaker.

Do not administer morphine sulfate extended-release capsules pellets through a nasogastric tube.

3 DOSAGE FORMS AND STRENGTHS

Morphine sulfate extended-release capsules contains white to off-white or tan colored polymer coated pellets, have an outer opaque capsule with colors as identified below and are available in six dose strengths:
Each 20 mg extended-release capsule has a yellow opaque cap printed with "KADIAN" and a yellow opaque body printed with "20 mg".
Each 30 mg extended-release capsule has a blue violet opaque cap printed with "KADIAN" and a blue violet opaque body printed with "30 mg".
Each 50 mg extended-release capsule has a blue opaque cap printed with "KADIAN" and a blue opaque body printed with "50 mg".
Each 60 mg extended-release capsule has a pink opaque cap printed with "KADIAN" and a pink opaque body printed with "60 mg".
Each 80 mg extended-release capsule has a light orange opaque cap printed with "KADIAN" and a light orange opaque body printed with "80 mg".
Each 100 mg extended-release capsule has a green opaque cap printed with "KADIAN" and a green opaque body printed with "100 mg".

4 CONTRAINDICATIONS

Morphine sulfate extended-release capsules is 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 Addiction, Abuse, and Misuse

Morphine sulfate extended-release capsules contains morphine, a Schedule II controlled substance. As an opioid, morphine sulfate extended-release capsules exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*. As modified-release products such as morphine sulfate extended-release capsules deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of morphine present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed morphine sulfate extended-release capsules and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing morphine sulfate extended-release capsules, and monitor all patients receiving morphine sulfate extended-release capsules 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 addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of morphine sulfate extended-release capsules for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as morphine sulfate extended-release capsules, but use in such patients necessitates intensive counseling about the risks and proper use of morphine sulfate extended-release capsules along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of morphine sulfate extended-release capsules by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of morphine and can result in overdose and death *[see Overdosage (10)]*.

Opioid agonists such as morphine sulfate extended-release capsules 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 capsules. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, 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 extended-release capsules, 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 capsules and following dose increases.

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

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

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of morphine sulfate extended-release capsules during pregnancy can result in withdrawal signs 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. 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.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.4 Interactions with Central Nervous System Depressants

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on morphine sulfate extended-release capsules therapy. The co-ingestion of alcohol with morphine sulfate extended-release capsules may result in increased plasma levels and a potentially fatal overdose of morphine *[see Clinical Pharmacology (12.3)]*.

Hypotension, profound sedation, coma, respiratory depression, and death may result if morphine sulfate extended-release capsules is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of morphine sulfate extended-release capsules in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin morphine sulfate extended-release capsules is made, start with a low dose of morphine sulfate extended-release capsules (30 mg or lower) every 24 hours, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7)]*.

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening 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. Monitor such patients closely, particularly when initiating and titrating morphine sulfate extended-release capsules and when morphine sulfate extended-release capsules is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*.

5.6 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 capsules, as in these patients, even usual therapeutic doses of morphine sulfate extended-release capsules 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.

5.7 Hypotensive Effect

Morphine sulfate extended-release capsules 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 (7.2)]*. Monitor these patients for signs of hypotension after initiating or titrating the dose of morphine sulfate extended-release capsules. In patients with circulatory shock, morphine sulfate extended-release capsules may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of morphine sulfate extended-release capsules in patients with circulatory shock.

5.8 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking morphine sulfate extended-release capsules who may be susceptible to the intracranial effects of CO_2 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 capsules. Morphine sulfate extended-release capsules may reduce respiratory drive, and the resultant CO_2 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 capsules in patients with impaired consciousness or coma.

5.9 Use in Patients with Gastrointestinal Conditions

Morphine sulfate extended-release capsules is contraindicated in patients with paralytic ileus. Avoid the use of Morphine Sulfate in patients with other GI obstruction.

The morphine in morphine sulfate extended-release capsules 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 capsules 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 capsules therapy.

5.11 Avoidance of Withdrawal

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

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

5.12 Driving and Operating Machinery

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

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Hypotensive Effect *[see Warnings and Precautions (5.7)]*
- Gastrointestinal Effects *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*

In the randomized study, the most common adverse reactions with morphine sulfate extended-release capsules therapy were drowsiness, constipation, nausea, dizziness, and anxiety. The most common adverse reactions leading to study discontinuation were nausea, constipation (may be severe), vomiting, fatigue, dizziness, pruritus, and somnolence.

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical trial patients with chronic cancer pain (n = 227) (AE by Body System as seen in 2% or more of patients)	Percentage %
CENTRAL NERVOUS SYSTEM	**28**
Drowsiness	9
Dizziness	6
Anxiety	5
Confusion	4
Dry mouth	3
Tremor	2
GASTROINTESTINAL	**26**
Constipation	9
Nausea	7
Diarrhea	3
Anorexia	3
Abdominal pain	3
Vomiting	2
BODY AS A WHOLE	**16**
Pain	3
Disease progression	3
Chest pain	2
Diaphoresis	2
Fever	2
Asthenia	2
Accidental injury	2
RESPIRATORY	**3**
Dyspnea	3
SKIN & APPENDAGES	**3**
Rash	3
METABOLIC & NUTRITIONAL	**3**
Peripheral edema	3
HEMIC & LYMPHATIC	**4**
Anemia	2
Leukopenia	2

Medication Guide
Morphine Sulfate
Extended-Release Capsules, USP

CII

Morphine sulfate extended-release capsules are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) 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.
- Not for use to treat pain that is not around-the-clock.

Important information about morphine sulfate extended-release capsules:

- **Get emergency help right away if you take too much morphine sulfate extended-release capsules (overdose).** When you first start taking morphine sulfate extended-release capsules, 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.
- Never give anyone else your morphine sulfate extended-release capsules. They could die from taking it. Store morphine sulfate extended-release capsules away from children and in a safe place to prevent stealing or abuse. Selling or giving away morphine sulfate extended-release capsules is against the law.

Do not take morphine sulfate extended-release capsules 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 extended-release capsules, 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 extended-release capsules during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Morphine sulfate extended-release capsules passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking morphine sulfate extended-release capsules with certain other medicines can cause serious side effects.

When taking morphine sulfate extended-release capsules:

- Do not change your dose. Take morphine sulfate extended-release capsules exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 12 or 24 hours at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time.
- Swallow morphine sulfate extended-release capsules whole. Do not cut, break, chew, crush, dissolve, snort, or inject morphine sulfate extended-release capsules because this may cause you to overdose and die.
- You should not receive morphine sulfate extended-release capsules through a nasogastric tube.
- If you cannot swallow morphine sulfate extended-release capsules, see the detailed Instructions for Use.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking morphine sulfate extended-release capsules without talking to your healthcare provider.**
- After you stop taking morphine sulfate extended-release capsules, flush any unused capsules down the toilet.

While taking morphine sulfate extended-release capsules DO NOT:

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

The possible side effects of morphine sulfate extended-release capsules 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, light-headedness when changing positions, or you are feeling faint.

These are not all the possible side effects of morphine sulfate extended-release capsules. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or call Par Pharmaceutical, Inc. at 1800-828-9393. **For more information go to dailymed.nlm.nih.gov**

Manufactured for:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977 U.S.A.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: July 2014

Instructions For Use
Morphine Sulfate Extended-Release Capsules, USP

C II

If you cannot swallow morphine sulfate extended-release capsules, tell your healthcare provider. There may be another way to take morphine sulfate extended-release capsules that may be right for you. If your healthcare provider tells you that you can take morphine sulfate extended-release capsules using this other way, follow these steps:

Morphine sulfate extended-release capsules can be opened and the pellets inside the capsule can be sprinkled over applesauce, as follows:

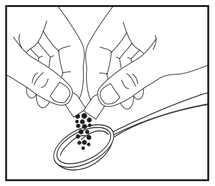

Figure 1

- Open the morphine sulfate extended-release capsules and sprinkle the pellets over about one tablespoon of applesauce *(See Figure 1)*.

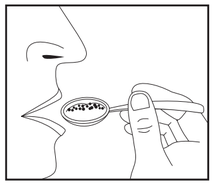

Figure 2

- Swallow all of the applesauce and pellets right away. Do not save any of the applesauce and pellets for another dose *(See Figure 2)*.

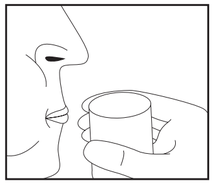

Figure 3

- Rinse your mouth to make sure you have swallowed all of the pellets. Do not chew the pellets *(See Figure 3)*.

Figure 4

- Flush the empty capsule down the toilet right away *(See Figure 4)*.

You should not receive morphine sulfate extended-release capsules through a nasogastric tube.

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In clinical trials in patients with chronic cancer pain, the most common adverse events reported by patients at least once during therapy were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%), and anxiety (6%). Other less common side effects expected from morphine sulfate extended-release capsules or seen in less than 2% of patients in the clinical trials were:

- Body as a Whole: Headache, chills, flu syndrome, back pain, malaise, withdrawal syndrome
- Cardiovascular: Tachycardia, atrial fibrillation, hypotension, hypertension, pallor, facial flushing, palpitations, bradycardia, syncope
- Central Nervous System: Confusion, anxiety, abnormal thinking, abnormal dreams, lethargy, depression, loss of concentration, insomnia, amnesia, paresthesia, agitation, vertigo, foot drop, ataxia, hypesthesia, slurred speech, hallucinations, vasodilation, euphoria, apathy, seizures, myoclonus
- Endocrine: Hyponatremia due to inappropriate ADH secretion, gynecomastia
- Gastrointestinal: Dysphagia, dyspepsia, stomach atony disorder, gastro-esophageal reflux, delayed gastric emptying, biliary colic
- Hemic and Lymphatic: Thrombocytopenia
- Metabolic and Nutritional: Hyponatremia, edema
- Musculoskeletal: Back pain, bone pain, arthralgia
- Respiratory: Hiccup, rhinitis, atelectasis, asthma, hypoxia, respiratory insufficiency, voice alteration, depressed cough reflex, non-cardiogenic pulmonary edema
- Skin and Appendages: Decubitus ulcer, pruritus, skin flush
- Special Senses: Amblyopia, conjunctivitis, miosis, blurred vision, nystagmus, diplopia
- Urogenital: Urinary abnormality, amenorrhea, urinary retention, urinary hesitancy, reduced libido, reduced potency, prolonged labor

Four-Week Open-Label Safety Study
In the open-label, 4-week safety study, 1418 patients ages 18 to 85 with chronic, non-malignant pain (e.g., back pain, osteoarthritis, neuropathic pain) were enrolled. The most common adverse events reported at least once during therapy were constipation (12%), nausea (9%), and somnolence (3%). Other less common side effects occurring in less than 3% of patients were vomiting, pruritus, dizziness, sedation, dry mouth, headache, fatigue, and rash.

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

7 DRUG INTERACTIONS
7.1 Alcohol
Concomitant use of alcohol with morphine sulfate extended-release capsules can result in an increase of morphine plasma levels and potentially fatal overdose of morphine. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on morphine sulfate extended-release capsules therapy *[See Clinical Pharmacology (12.3)]*.

7.2 CNS Depressants
The concomitant use of morphine sulfate extended-release capsules with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and morphine sulfate extended-release capsules for signs of respiratory depression, sedation and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.2)* and *Warnings and Precautions (5.4)]*.

7.3 Interactions with Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics
Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of morphine sulfate extended-release capsules or precipitate withdrawal symptoms. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving morphine sulfate extended-release capsules.

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

7.5 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 capsules for increased respiratory and central nervous system depression. Morphine sulfate extended-release capsules should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

7.6 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 capsules and cimetidine are used concurrently.

7.7 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.

7.8 Anticholinergics
Anticholinergics or other drugs 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 capsules is used concurrently with anticholinergic drugs.

7.9 P-Glycoprotein (PGP) Inhibitors
PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine by about two-fold. Monitor patients for signs of respiratory and central nervous system depression when PGP inhibitors are used concurrently with morphine sulfate extended-release capsules.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

Teratogenic Effects (Pregnancy Category C)
There are no adequate and well-controlled studies in pregnant women. Morphine sulfate extended-release capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 sternebrae, 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.

Nonteratogenic Effects
Infants born to mothers who have taken opioids chronically may exhibit neonatal withdrawal syndrome *[see Warnings and Precautions (5.3)]*, reversible reduction in brain volume, small size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. Morphine sulfate extended-release capsules 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 and Delivery
Opioids cross the placenta and may produce respiratory depression in neonates. Morphine sulfate extended-release capsules is not for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics 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.

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 symptoms 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 capsules, 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 efficacy of morphine sulfate extended-release capsules in patients less than 18 years have not been established.

8.5 Geriatric Use
Clinical studies of morphine sulfate extended-release capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Morphine sulfate extended-release capsules contains 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 capsules can be abused and is 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 capsules, 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 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 reduce abuse of opioid drugs.

Risks Specific to Abuse of Morphine Sulfate Extended-Release Capsules
Morphine sulfate extended-release capsules is for oral use only. Abuse of morphine sulfate extended-release capsules poses a risk of overdose and death. This risk is increased with concurrent abuse of morphine sulfate extended-release capsules with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved morphine sulfate extended-release capsules enhances drug release and increases the risk of over dose and death.

Due to the presence of talc as one of the excipients in morphine sulfate extended-release capsules, 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, mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Morphine sulfate extended-release capsules should not be abruptly discontinued *[see Dosage and Administration (2.3)]*. If morphine sulfate extended-release capsules is 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 symptoms *[see Use in Specific Populations (8.2)* and *Warnings and Precautions (5.3)]*.

10 OVERDOSAGE
Clinical Presentation
Acute overdosage with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, 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 cases of overdose, priorities are the re-establishment of a patent airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of cardiac and/or pulmonary failure as needed. 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 patients who are known, or suspected to be, physically dependent on morphine sulfate extended-release capsules. 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 capsules, carefully monitor the patient until spontaneous respiration is reliably re-established. Morphine sulfate extended-release capsules will continue to release morphine adding to the morphine load for up to 24 hours after administration, necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given 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. The severity of the withdrawal produced 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.

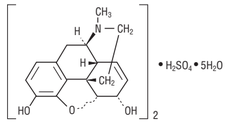
11 DESCRIPTION
Morphine sulfate extended-release capsules are for oral use and contain pellets of morphine sulfate. Morphine sulfate is an agonist at the mu-opioid receptor.

Each morphine sulfate extended-release capsule contains either 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg of morphine sulfate USP and the following inactive ingredients common to all strengths: hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, corn starch, and sucrose.

The capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and black ink, D&C yellow #10 (20 mg), FD&C red #3, FD&C blue #1 (30 mg), D&C red #28, FD&C red #40, FD&C blue #1 (50 mg), D&C red #28, FD&C red #40, FD&C blue #1 (60 mg), FD&C blue #1, FD&C red #40, FD&C yellow #6 (80 mg), D&C yellow #10, FD&C blue #1 (100 mg). The imprint ink contains black iron oxide, potassium hydroxide, propylene glycol, and shellac.

The chemical name of morphine sulfate is 7,8-didehydro-4,5 α- epoxy-17-methyl-morphinan-3,6 α- diol sulfate (2:1) (salt) pentahydrate. The empirical formula is $(C_{17}H_{19}NO_3)_2 \bullet H_2SO_4 \bullet 5H_2O$ and its molecular weight is 758.85.

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.

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. The effective dose in opioid-tolerant patients may be 10 to 50 times as great (or greater) than the appropriate dose for opioid-naïve individuals. 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 capsules is used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Effects on the Central Nervous System
The principal actions of therapeutic value of morphine are analgesia and sedation. Specific CNS opiate receptors and endogenous compounds with morphine-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, and little tolerance develops to this effect. 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 with worsening hypoxia in the setting of morphine overdose.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in 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 is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Effects on the Cardiovascular System
Morphine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Release of histamine may be induced by morphine and can contribute to opioid-induced hypotension. Manifestations of histamine release or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

Effects on the Endocrine System
Opioids inhibit the secretion of ACTH, cortisol, 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.

12.3 Pharmacokinetics
Absorption
Morphine sulfate extended-release capsules contain polymer coated extended-release pellets of morphine sulfate that release morphine significantly more slowly than oral morphine solution. Following the administration of oral morphine solution, approximately 50% of the morphine absorbed reaches the systemic circulation within 30 minutes compared to 8 hours with an equal amount of morphine sulfate extended-release capsules. Because of pre-systemic elimination, only about 20 to 40% of the administered dose reaches the systemic circulation.

Both dose-normalized C_{max} and dose-normalized $AUC_{0\text{-}48hr}$ values of morphine after a single dose administration of morphine sulfate extended-release capsules in healthy volunteers are less than those for morphine oral solution or an extended-release tablet formulation (Table 1).

When morphine sulfate extended-release capsules was given twice daily to 24 patients with chronic pain due to malignancy, steady-state was achieved in about two days. At steady-state, morphine sulfate extended-release capsules has a significantly lower C_{max} and a higher C_{min} than equivalent doses of oral morphine solution given every 4 hrs and an extended-release tablet given twice daily. When given once daily to 24 patients with malignancy, morphine sulfate extended-release capsules had a similar C_{max} and higher C_{min} at steady-state when compared to an extended-release morphine tablets, given twice daily at an equivalent total daily dosage (see Table 1).

The single-dose pharmacokinetics of morphine sulfate extended-release capsules are linear over the dosage range of 30 to 100 mg.

Table 1: Mean pharmacokinetic parameters (% coefficient variation) resulting from a fasting single dose study in normal volunteers and a multiple-dose study in patients with cancer pain.

Regimen/Dosage Form	AUC#,+ (ng•h/mL)	C_{max}+ (ng/mL)	T_{max} (h)	C_{min}+ (ng/mL)	Fluctuation*
Single Dose (n = 24)					
Morphine sulfate extended-release capsules	271.0 (19.4)	15.6 (24.4)	8.6 (41.1)	na^	na
Extended-release tablet	304.3 (19.1)	30.5 (32.1)	2.5 (52.6)	na	na
Morphine solution	362.4 (42.6)	64.4 (38.2)	0.9 (55.8)	na	na
Multiple Dose (n = 24)					
Morphine sulfate extended-release capsules once daily	500.9 (38.6)	37.3 (37.7)	10.3 (32.2)	9.9 (52.3)	3.0 (45.5)
Extended-release tablet twice daily	457.3 (40.2)	36.9 (42.0)	4.4 (53.0)	7.6 (60.3)	4.1 (51.5)

For single dose AUC = $AUC_{0\text{-}48hr}$, for multiple dose AUC = $AUC_{0\text{-}24hr}$ at steady-state
+ For single dose parameter normalized to 100 mg, for multiple dose parameter normalized to 100 mg per 24 hours
* Steady-state fluctuation in plasma concentrations = C_{max}-C_{min}/C_{min}
^ Not applicable

Food effect: While concurrent administration of food slows the rate of absorption of morphine sulfate extended-release capsules, the extent of absorption is not affected and morphine sulfate extended-release capsules can be administered without regard to meals.

Distribution
Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. The volume of distribution of morphine is approximately 3 to 4 L/kg. Morphine is 30 to 35% reversibly bound to plasma proteins. Although the primary site of action of morphine is in the CNS, only small quantities pass the blood-brain barrier. Morphine also crosses the placental membranes *[see Use in Specific Populations (8.1)]* and has been found in breast milk *[see Use in Specific Populations (8.3)]*.

Metabolism
Major pathways of morphine metabolism include glucuronidation in the liver 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. M3G has no significant contribution to the analgesic activity. Although M6G does not readily cross the blood-brain barrier, it has been shown to have opioid agonist and analgesic activity in humans.

Studies in healthy subjects and cancer patients have shown that the glucuronide metabolite to morphine mean molar ratios (based on AUC) are similar after both single doses and at steady-state for morphine sulfate extended-release capsules, 12-hour extended-release morphine sulfate tablets and morphine sulfate solution.

Excretion
Approximately 10% of a morphine dose is excreted unchanged in the urine. Most of the dose is excreted in the urine as M3G and M6G which are then renally excreted. A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic cycling. Seven to 10% of administered morphine is excreted in the feces.

The mean adult plasma clearance of morphine is about 20 to 30 mL/minute/kg. The effective terminal half-life of morphine after IV administration is reported to be approximately 2 hours. The terminal elimination half-life of morphine following a single dose of morphine sulfate extended-release capsules administration is approximately 11 to 13 hours.

Specific Populations
Geriatric Patients: The pharmacokinetics of morphine sulfate extended-release capsules have not been investigated in elderly patients (>65 years) although such patients were included in the clinical studies.

Pediatric Patients: The pharmacokinetics of morphine sulfate extended-release capsules have not been evaluated in a pediatric population.

Gender: No meaningful differences between male and female patients were demonstrated in the analysis of the pharmacokinetic data from clinical studies.

Race: Chinese subjects given intravenous morphine in one study had a higher clearance when compared to Caucasian subjects (1852 ± 116 mL/min versus 1495 ± 80 mL/min).

Hepatic Impairment: The pharmacokinetics of morphine were found to be significantly altered in individuals with alcoholic cirrhosis. The 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 patients indicating a decrease in metabolic activity. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted.

Renal Impairment: The pharmacokinetics of morphine are altered in patients with renal failure. The AUC is increased and clearance is decreased. Metabolites, M3G and M6G accumulate several fold in patients with renal failure compared to healthy subjects. 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 capsules contain white to off-white or tan colored polymer coated extended-release pellets of morphine sulfate and are available in six dose strengths.

	Morphine Sulfate Extended-Release Capsules 20 mg	Morphine Sulfate Extended-Release Capsules 30 mg	Morphine Sulfate Extended-Release Capsules 50 mg
Extended-Release Capsule Description	size 4, yellow opaque cap printed with "KADIAN" and yellow opaque body printed with "20 mg".	size 4, blue violet opaque cap printed with "KADIAN" and blue violet opaque body printed with "30 mg".	size 2, blue opaque cap printed with "KADIAN" and blue opaque body printed with "50 mg".
Bottle Size	100	100	100
NDC #	NDC 49884-833-01	NDC 49884-834-01	NDC 49884-835-01

	Morphine Sulfate Extended-Release Capsules 60 mg	Morphine Sulfate Extended-Release Capsules 80 mg	Morphine Sulfate Extended-Release Capsules 100 mg
Extended-Release Capsule Description	size 1, pink opaque cap printed with "KADIAN" and pink opaque body printed with "60 mg".	size 0, light orange opaque cap printed with "KADIAN" and light orange opaque body printed with "80 mg".	size 0, green opaque cap printed with "KADIAN" and green opaque body printed with "100 mg".
Bottle Size	100	100	100
NDC #	NDC 49884-836-01	NDC 49884-837-01	NDC 49884-838-01

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Protect from light and moisture. Dispense in a sealed tamper-evident, childproof, light-resistant container.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse
Inform patients that the use of morphine sulfate extended-release capsules, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share morphine sulfate extended-release capsules with others and to take steps to protect morphine sulfate extended-release capsules 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 extended-release capsules or when the dose is increased, and that it can occur even at recommended doses *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

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

Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that prolonged use of morphine sulfate extended-release capsules during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3)]*.

Interactions with Alcohol and other CNS Depressants
Instruct patients not to consume alcoholic beverages, as well as prescription and over-the counter products that contain alcohol, during treatment with morphine sulfate extended-release capsules. The co-ingestion of alcohol with morphine sulfate extended-release capsules may result in increased plasma levels and a potentially fatal overdose of morphine *[see Warnings and Precautions (5.4)]*.

Inform patients that potentially serious additive effects may occur if morphine sulfate extended-release capsules is used with alcohol or 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 capsules, including the following:

- Swallowing morphine sulfate extended-release capsules whole or sprinkling the capsule contents on applesauce and then swallowing without chewing
- Not crushing, chewing, or dissolving the pellets in the capsules
- Using morphine sulfate extended-release capsules exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Not discontinuing morphine sulfate extended-release capsules without first discussing the need for a tapering regimen with the prescriber

Hypotension
Inform patients that morphine sulfate extended-release capsules 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 capsules 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 morphine sulfate extended-release capsules. Advise patients how to recognize such a reaction and when to seek medical attention.

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

Disposal of Unused Morphine Sulfate Extended-Release Capsules
Advise patients to flush the unused capsules down the toilet when morphine sulfate extended-release capsules is no longer needed.

For all medical inquiries contact:
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