MORPHINE SULFATE- morphine sulfate capsule, extended release
Actavis Pharma, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
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, CII
(Once Daily)

Initial U.S. Approval: 1941

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **Morphine Sulfate Extended-Release Capsules expose 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 these behaviors and conditions. (5.1)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)**
- **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. (5.3)**
- **Accidental ingestion of Morphine Sulfate Extended-Release Capsules, especially by 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 prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **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. (5.5)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5, 7)**

INDICATIONS AND USAGE

Morphine Sulfate Extended-Release Capsules are 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. (1)

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.(1)
- Morphine Sulfate Extended-Release Capsules are not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- Morphine Sulfate Extended-Release 90 mg and 120 mg capsules, are only for use in patients in whom tolerance to an opioid of comparable potency is established.
- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg of

morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg of oral oxycodone per day, 8 mg of oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Must swallow Morphine Sulfate Extended-Release Capsules intact, or sprinkle the capsule contents on applesauce and immediately swallow. (2.1, 2.5)
- Do not cut, break, chew, crush, or dissolve the pellets in Morphine Sulfate Extended-Release Capsules (risk of potentially fatal overdose) (2.1, 2.5, 5.1)
- For opioid-naïve and opioid non-tolerant patients, initiate with 30 mg capsules orally every 24 hours. Dose can be increased every 3 to 4 days using increments of 30 mg. (2.1, 2.2)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with Morphine Sulfate Extended-Release Capsules. Consider prescribing naloxone based on the patient's risk factors for overdose (2.2, 5.1, 5.3, 5.5).

- Do not abruptly discontinue Morphine Sulfate Extended-Release Capsules in a physically-dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.3, 2.4, 5.13)

DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, 120 mg (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dose initiation and titration. Avoid use of Morphine Sulfate Extended-Release Capsules in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of Morphine Sulfate Extended-Release Capsules in patients with impaired consciousness or coma. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (greater than or equal to 10%) are constipation, nausea, somnolence, vomiting and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva at 1-888-838-2872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue Morphine Sulfate Extended-Release Capsules if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with mixed agonist/antagonist because they may reduce analgesic effect of Morphine Sulfate Extended-Release Capsules or precipitate withdrawal symptoms. (5.13, 7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS

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 and conditions *[see Warnings and Precautions (5.1)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

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

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

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Morphine Sulfate 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; or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing, or dissolving the pellets in Morphine Sulfate Extended-Release Capsules can cause rapid release and absorption of a potentially fatal dose of morphine *[see Warnings and Precautions (5.3)]*.

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 (5.3)]*.

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 (5.4)]*.

Interaction with Alcohol
Instruct patients not to consume alcoholic beverages or use prescription or non-prescription 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 (5.5)].*

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

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

1 INDICATIONS AND USAGE

Morphine Sulfate Extended-Release Capsules are 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 *[see Warnings and Precautions (5.1)]*, 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 are not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

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 90 mg and 120 mg capsules are only for use in 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 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, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

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

- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with Morphine Sulfate Extended-Release Capsules and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.
- Instruct patients to swallow Morphine Sulfate Extended-Release Capsules whole *[see Patient Counseling Information (17)]*. 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 (5.1)]*.
- Instruct patients who are unable to swallow Morphine Sulfate Extended-Release Capsules to sprinkle the capsule contents on applesauce and immediately swallow without chewing *[see Dosage and Administration (2.5)]*.

Morphine Sulfate Extended-Release Capsules are administered at a frequency of once daily (every 24 hours).

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Morphine Sulfate Extended-Release Capsules *[see Warnings and Precautions (5.3), Patient Counseling Information (17)].*

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient’s risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see Warnings and Precautions (5.1, 5.3, 5.5)].*

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

2.3 Initial Dosing

Use of Morphine Sulfate Extended-Release Capsules as the First Opioid Analgesic (opioid-naïve patients)

Initiate treatment with Morphine Sulfate Extended-Release Capsules with a 30 mg capsule orally every 24 hours. Adjust the dose of Morphine Sulfate Extended-Release Capsules in increments not greater than 30 mg every 3 to 4 days.

Use of Morphine Sulfate Extended-Release Capsules in Patients who are not Opioid Tolerant (opioid non-tolerant patients)

The starting dose of Morphine Sulfate Extended-Release Capsules for patients who are not opioid tolerant is 30 mg orally every 24 hours.

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

Discontinue all other around-the-clock opioid drugs when Morphine Sulfate Extended-

Release Capsules therapy is initiated.

There are no established conversion ratios from other opioids to Morphine Sulfate Extended-Release Capsules defined by clinical trials. Initiate dosing using Morphine Sulfate Extended-Release Capsules 30 mg orally every 24 hours.

It is safer to underestimate a patient's 24-hour oral morphine dosage and provide rescue medication (e.g. immediate-release morphine) than to overestimate the 24-hour oral morphine dosage and manage an adverse reaction due to an overdose. While useful tables of opioid equivalents are readily available, there is inter-patient variability in the potency of opioid drugs and formulations.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to Morphine Sulfate Extended-Release Capsules.

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 the patient's total daily oral morphine dose as Morphine Sulfate Extended-Release Capsules once-daily. Monitor patients closely when initiating Morphine Sulfate Extended-Release Capsule therapy and adjust the dosage of Morphine Sulfate Extended-Release Capsules as needed. Morphine Sulfate Extended-Release Capsules should not be given more frequently than every 24 hours.

Conversion from Parenteral Morphine or Other Non-Morphine Opioids (Parenteral or Oral) 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 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.

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.

The first dose of Morphine Sulfate Extended-Release Capsules 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 Capsules formulation.

2.4 Titration and Maintenance of Therapy

Individually titrate Morphine Sulfate Extended-Release Capsules to a dose that provides adequate analgesia and minimizes adverse reactions. 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 *[see Warnings and Precautions (5.1)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

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 dosage. Because steady-state plasma concentrations are approximated within 2 to 3 days, Morphine Sulfate Extended-Release Capsules dosage adjustments may be done every 3 to 4 days.

The daily dose of Morphine Sulfate Extended-Release Capsules must be limited to a maximum of 1600 mg/day. Morphine Sulfate Extended-Release Capsules doses of over 1600 mg/day contain a quantity of fumaric acid that has not been demonstrated to be safe, and which may result in serious renal toxicity.

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

2.5 Safe Reduction or Discontinuation of Morphine Sulfate Extended-Release Capsules

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

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

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

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal

symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.3)]*.

2.6 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 (5.1)]*.

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.

Do not administer Morphine Sulfate Extended-Release Capsules pellets through a nasogastric or gastric tubes.

3 DOSAGE FORMS AND STRENGTHS

Morphine Sulfate Extended-Release Capsules, USP (once daily) contain pellets of morphine sulfate and are available as follows:

30 mg capsule has a dark blue opaque cap and body, printed with and 3090 on both the cap and body in black ink.

45 mg capsule has a violet opaque cap and body, printed with and 3116 on both the cap and body in black ink.

60 mg capsule has a light green opaque cap and body, printed with and 3091 on both the cap and body in black ink.

75 mg capsule has a brown opaque cap and body, printed with and 3117 on both the cap and body in black ink.

90 mg capsule has a green opaque cap and body, printed with and 3092 on both the cap and body in black ink.

120 mg capsule has a light blue opaque cap and body, printed with and 3093 on both the cap and body in black ink.

4 CONTRAINDICATIONS

Morphine Sulfate Extended-Release Capsules are contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.6)]*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Warnings and Precautions (5.7)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.11)]*
- 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 contain morphine, a Schedule II controlled substance. As an opioid, Morphine Sulfate Extended-Release Capsules exposes users to the risks of addiction, abuse, and misuse. Because extended-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 *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Morphine Sulfate Extended-Release Capsules. 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 and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent Morphine Sulfate Extended-Release Capsules the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids 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. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

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 the morphine and can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Morphine Sulfate 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 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant

education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

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

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

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death.

Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[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 dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of Morphine Sulfate Extended-Release Capsules.

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.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Patient Counseling Information (17)].*

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.5)].*

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Morphine Sulfate Extended-Release

Capsules. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered *[see Patient Counseling Information (17)].*

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone. *[see Warnings and Precautions (5.1, 5.5, Patient Counseling Information (17)].*

5.4 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.5 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

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)]*.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Morphine Sulfate Extended-Release Capsules with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Morphine Sulfate Extended-Release Capsules is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

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

The use of Morphine Sulfate Extended-Release Capsules in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: Morphine Sulfate Extended-Release Capsules-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of Morphine Sulfate Extended-Release Capsules *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.3)]*.

Monitor such patients closely, particularly when initiating and titrating Morphine Sulfate Extended-Release Capsules and when Morphine Sulfate Extended-Release Capsules are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.3)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.7 Interaction with Monoamine Oxidase Inhibitors

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

5.8 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one 1 month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.9 Severe Hypotension

Morphine Sulfate 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)]*. 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.

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

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

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.

5.11 Risks of Use in Patients with Gastrointestinal Conditions

Morphine Sulfate Extended-Release Capsules are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The morphine in Morphine Sulfate Extended-Release Capsules may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders

The morphine in Morphine Sulfate Extended-Release Capsules may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Morphine Sulfate Extended-Release Capsules therapy.

5.13 Withdrawal

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

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including Morphine Sulfate Extended-Release Capsules. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal *symptoms [see Drug Interactions (7)]*.

5.14 Risks of Driving and Operating Machinery

Morphine Sulfate 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 *[see Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

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

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.5)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.8)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Withdrawal *[see Warnings and Precautions (5.13)]*

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.

In controlled and open-label clinical studies, 560 patients with chronic malignant or non-malignant pain were treated with Morphine Sulfate Extended-Release Capsules. The most common serious adverse events reported with administration of Morphine Sulfate Extended-Release Capsules were vomiting, nausea, death, dehydration, dyspnea, and sepsis. (Deaths occurred in patients treated for pain due to underlying malignancy.) Serious adverse events caused by morphine include respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most common adverse events (seen in greater than 10%) reported by patients treated with Morphine Sulfate Extended-Release Capsules during the clinical trials at least once during therapy were constipation, nausea, somnolence, vomiting, and headache. Adverse events occurring in 5 to 10% of study patients were peripheral edema, diarrhea, abdominal pain, infection, urinary tract infection, accidental injury, flu syndrome, back pain, rash, sweating, fever, insomnia, depression, paresthesia, anorexia, dry mouth, asthenia and dyspnea. Other less common side effects expected from opioid analgesics, including morphine, or seen in fewer than 5% of patients taking Morphine Sulfate Extended-Release Capsules in the clinical trials were:

Body as a Whole: malaise, withdrawal syndrome.

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

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

Hemic and Lymphatic System: anemia, thrombocytopenia.

Metabolic and Nutritional Disorders: edema, weight loss.

Musculoskeletal: skeletal muscle rigidity.

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

Respiratory System: hiccup, hypoventilation, voice alteration.

Skin and Appendages: dry skin, urticaria.

Special Senses: amblyopia, eye pain, taste perversion.

Urogenital System: abnormal ejaculation, dysuria, impotence, decreased libido, oliguria, urinary retention.

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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of morphine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Morphine Sulfate Extended-Release Capsules.

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

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with Morphine Sulfate Extended-Release Capsules.

Table 1: Clinically Significant Drug Interactions with Morphine Sulfate Extended-Release Capsules

Alcohol	
Clinical Impact:	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.
Intervention:	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)]*.
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepine or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are

Intervention:	inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3, 5.5)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers and muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Morphine Sulfate Extended-Release Capsules if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT_3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*.
Intervention:	Do not use Morphine Sulfate Extended-Release Capsules in patients taking MAOIs or within 14 days of stopping such treatment.
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of Morphine Sulfate Extended-Release Capsules and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Morphine Sulfate Extended-Release Capsules and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3, 5.5)]*
Cimetidine	
Clinical Impact:	The concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma, and death.
	Monitor patients for signs of respiratory depression that may

Intervention:	be greater than otherwise expected and decrease the dosage of Morphine Sulfate Extended-Release Capsules and/or cimetidine as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when Morphine Sulfate Extended-Release Capsules are used concomitantly with anticholinergic drugs.
P-Glycoprotein (PGP) Inhibitors	
Clinical Impact:	The concomitant use of PGP-inhibitors can increase the exposure to morphine by about two-fold and can increase risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Morphine Sulfate Extended-Release Capsules and/or the PGP-inhibitor as necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. There are no available data with Morphine Sulfate Extended-Release Capsules in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Published studies with morphine use during pregnancy have not reported a clear association with morphine and major birth defects *[see Human Data]*.

In published animal reproduction studies, morphine administered subcutaneously during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) at 5 and 16 times the human daily dose of 60 mg based on body surface area (HDD) in hamsters and mice, respectively, lower fetal body weight and increased incidence of abortion at 0.4 times the HDD in the rabbit, growth retardation at 6 times the HDD in the rat, and axial skeletal fusion and cryptorchidism at 16 times the HDD in the mouse.

Administration of morphine sulfate to pregnant rats during organogenesis and through lactation resulted in cyanosis, hypothermia, decreased brain weights, pup mortality, decreased pup body weights, and adverse effects on reproductive tissues at 3 to 4 times the HDD; and long-term neurochemical changes in the brain of offspring which correlate with altered behavioral responses that persist through adulthood at exposures comparable to and less than the HDD *[see Animal Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

Labor or Delivery

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

Data

Human Data

The results from a population-based prospective cohort, including 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any time during pregnancy, indicate no increased risk for congenital malformations. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design.

Animal Data

Formal reproductive and developmental toxicology studies for morphine have not been conducted. Exposure margins for the following published study reports are based on human daily dose of 60 mg morphine using a body surface area comparison (HDD).

Neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of morphine sulfate (35 to 322 mg/kg) on Gestation Day 8 to pregnant hamsters (4.7 to 43.5 times the HDD). A no adverse effect level was not defined in this study and the findings cannot be clearly attributed to maternal toxicity. Neural tube defects (exencephaly), axial skeletal fusions, and cryptorchidism were reported following a single subcutaneous (SC) injection of morphine sulfate to pregnant mice (100 to 500 mg/kg) on Gestation Day 8 or 9 at 200 mg/kg or greater (16 times the HDD) and fetal resorption at 400 mg/kg or higher (32 times the HDD). No adverse effects were noted following 100 mg/kg morphine in this model (8 times the HDD). In one study, following continuous subcutaneous infusion of doses greater than or equal to 2.72 mg/kg to mice

(0.2 times the HDD), exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted. The effects were reduced with increasing daily dose; possibly due to rapid induction of tolerance under these infusion conditions. The clinical significance of this report is not clear.

Decreased fetal weights were observed in pregnant rats treated with 20 mg/kg/day morphine sulfate (3.2 times the HDD) from Gestation Day 7 to 9. There was no evidence of malformations despite maternal toxicity (10% mortality). In a second rat study, decreased fetal weight and increased incidences of growth retardation were noted at 35 mg/kg/day (5.7 times the HDD) and there was a reduced number of fetuses at 70 mg/kg/day (11.4 times the HDD) when pregnant rats were treated with 10, 35, or 70 mg/kg/day morphine sulfate via continuous infusion from Gestation Day 5 to 20. There was no evidence of fetal malformations or maternal toxicity.

An increased incidence of abortion was noted in a study in which pregnant rabbits were treated with 2.5 (0.8 times the HDD) to 10 mg/kg morphine sulfate via subcutaneous injection from Gestation Day 6 to 10. In a second study, decreased fetal body weights were reported following treatment of pregnant rabbits with increasing doses of morphine (10 to 50 mg/kg/day) during the pre-mating period and 50 mg/kg/day (16 times the HDD) throughout the gestation period. No overt malformations were reported in either publication; although only limited endpoints were evaluated.

In published studies in rats, exposure to morphine during gestation and/or lactation periods is associated with: decreased pup viability at 12.5 mg/kg/day or greater (2 times the HDD); decreased pup body weights at 15 mg/kg/day or greater (2.4 times the HDD); decreased litter size, decreased absolute brain and cerebellar weights, cyanosis, and hypothermia at 20 mg/kg/day (3.2 times the HDD); alteration of behavioral responses (play, social-interaction) at 1 mg/kg/day or greater (0.2 times the HDD); alteration of maternal behaviors (e.g., decreased nursing and pup retrievals) in mice at 1 mg/kg or higher (0.08 times the HDD) and rats at 1.5 mg/kg/day or higher (0.2 times the HDD); and a host of behavioral abnormalities in the offspring of rats, including altered responsiveness to opioids at 4 mg/kg/day (0.7 times the HDD) or greater.

Fetal and/or postnatal exposure to morphine in mice and rats has been shown to result in morphological changes in fetal and neonatal brain and neuronal cell loss, alteration of a number of neurotransmitter and neuromodulator systems, including opioid and non-opioid systems, and impairment in various learning and memory tests that appear to persist into adulthood. These studies were conducted with morphine treatment usually in the range of 4 to 20 mg/kg/day (0.7 to 3.2 times the HDD). Additionally, delayed sexual maturation and decreased sexual behaviors in female offspring at 20 mg/kg/day (3.2 times the HDD), and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed at 20 mg/kg/day (3.2 times the HDD). Decreased litter size and viability were observed in the offspring of male rats that were intraperitoneally administered morphine sulfate for 1 day prior to mating at 25 mg/kg/day (4.1 times the HDD) and mated to untreated females. Decreased viability and body weight and/or movement deficits in both first and second generation offspring were reported when male mice were treated for 5 days with escalating doses of 120 to 240 mg/kg/day morphine sulfate (9.7 to 19.5 times the HDD) or when female mice treated with escalating doses of 60 to 240 mg/kg/day (4.9 to 19.5 times the HDD) followed by a 5-day treatment-free recovery period prior to mating. Similar multigenerational findings were also seen in female rats pre-gestationally treated with escalating doses of 10 to 22 mg/kg/day morphine (1.6 to 3.6 times the HDD).

8.2 Lactation

Risk Summary

Morphine is present in breast milk. Published lactation studies report variable

concentrations of morphine in breast milk with administration of immediate-release morphine to nursing mothers in the early postpartum period with a milk-to-plasma morphine AUC ratio of 2.5:1 measured in one lactation study. However, there is insufficient information to determine the effects of morphine on the breastfed infant and the effects of morphine on milk production. Lactation studies have not been conducted with extended–release morphine, including Morphine Sulfate Extended-Release Capsules. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Morphine Sulfate Extended-Release Capsules.

Clinical Considerations

Monitor infants exposed to morphine through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of morphine is stopped, or when breastfeeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2)]*.

In published animal studies, morphine administration adversely effected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats *[see Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of Morphine Sulfate Extended-Release Capsules in pediatric patients below the age of 18 have not been established. The range of dose strengths available may not be appropriate for treatment of very young pediatric patients. Sprinkling on applesauce is **NOT** a suitable alternative for these patients.

8.5 Geriatric Use

The pharmacokinetics of Morphine Sulfate Extended-Release Capsules have not been studied in elderly patients. In clinical studies of Morphine Sulfate Extended-Release Capsules, 100 patients who received Morphine Sulfate Extended-Release Capsules were age 65 and over, including 37 patients were age 75 and over. No overall differences in safety were observed between these subjects and younger subjects *[see Clinical Pharmacology (12.3)]*.

Elderly patients (aged 65 years or older) may have increased sensitivity to morphine. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Morphine Sulfate Extended-Release Capsules slowly in geriatric patients and monitor for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.6)]*.

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

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

8.7 Renal Impairment

Morphine pharmacokinetics are altered in patients with renal failure. Start these patients with a lower than normal dosage of Morphine Sulfate Extended-Release Capsules and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Morphine Sulfate Extended-Release Capsules contain morphine, a Schedule II controlled substance.

9.2 Abuse

Morphine Sulfate Extended-Release Capsules contains morphine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone, and tapentadol. Morphine Sulfate 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.

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.

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

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Morphine Sulfate 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 and federal law, is strongly advised.

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

Risks Specific to Abuse of Morphine Sulfate Extended-Release Capsules

Morphine Sulfate Extended-Release Capsules are 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 central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved Morphine Sulfate Extended-Release Capsules enhances 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 Capsules, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, 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 is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

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

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

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 (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with Morphine Sulfate Extended-Release Capsules can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial and complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose

In cases of overdose, priorities are the re-establishment 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.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer and opioid antagonist.

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 and add to the morphine load for 36 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product’s prescribing information.

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

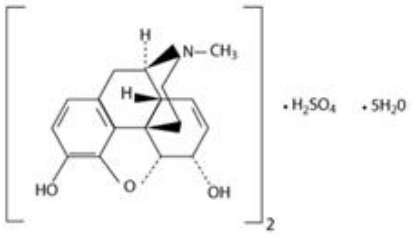
11 DESCRIPTION

Morphine Sulfate Extended-Release Capsules, USP (once daily) are for oral use and contain pellets of morphine sulfate, an opioid agonist.

Each Morphine Sulfate Extended-Release Capsule contains either 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, or 120 mg of morphine sulfate, USP and the following inactive ingredients: diethyl phthalate, ethylcellulose, gelatin, hydroxypropyl cellulose, methacrylic acid copolymer, polyethylene glycol, sugar spheres, talc, and titanium dioxide. The 30 mg capsules also contain FD&C blue #1. The 45 mg capsules also contain FD&C blue #1 and FD&C red #3. The 60 mg capsules also contain D&C yellow #10 and FD&C green #3. The 75 mg capsules also contain black iron oxide, red iron oxide, and yellow iron oxide. The 90 mg capsules also contain black iron oxide, FD&C blue #1, and yellow iron oxide. The 120 mg capsules also contain FD&C blue #1.The ink ingredients are common for all strengths: Tek-Print SW-9008 or SW-9009 black contains: black iron oxide, butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, and strong ammonia solution.

The chemical name of morphine sulfate is 7,8-didehydro-4,5 alpha-epoxy-17-methylmorphinan-3,6 alpha-diol sulfate (2:1) (salt) pentahydrate with a molecular weight of 758.83. The molecular formula is $(C_{17}H_{19}NO_3)_2 \bullet H_2SO_4 \bullet 5H_2O$.

Morphine sulfate is an odorless, white, crystalline powder. It is soluble in water and slightly soluble in alcohol, but is practically insoluble in chloroform or ether. The octanol: water partition coefficient of morphine is 1.42 at physiologic pH and the pKa is 7.9 for the tertiary nitrogen (the majority is ionized at pH 7.4). Its structural formula is:



USP dissolution test is pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Morphine is a full opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of morphine is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with morphine. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when Morphine Sulfate Extended-Release Capsules are used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Effects on the Central Nervous System

Morphine produces respiratory depression by direct action on brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to both increases in carbon dioxide tension and to electrical stimulation.

Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility and is associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm,

resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Morphine may also cause spasm of the sphincter of the urinary bladder.

Effects on the Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to hormonal changes that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of morphine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.2)]*.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing morphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.3)]*.

12.3 Pharmacokinetics

Absorption

Morphine Sulfate Extended-Release Capsules consist of two components, an immediate-release component and an extended-release component.

The oral bioavailability of morphine is less than 40% and shows large inter-individual variability due to extensive pre-systemic metabolism.

Following single-dose oral administration of a 60 mg dose of Morphine Sulfate Extended-Release Capsules under fasting conditions, morphine concentrations of approximately 3 to 6 ng/mL were achieved within 30 minutes after dosing and maintained for the 24-hour dosing interval. The pharmacokinetics of Morphine Sulfate Extended-Release Capsules were shown to be dose-proportional over a single oral dose range of 30 to 120 mg in

healthy volunteers and a multiple oral dose range of at least 30 to 180 mg in patients with chronic moderate to severe pain.

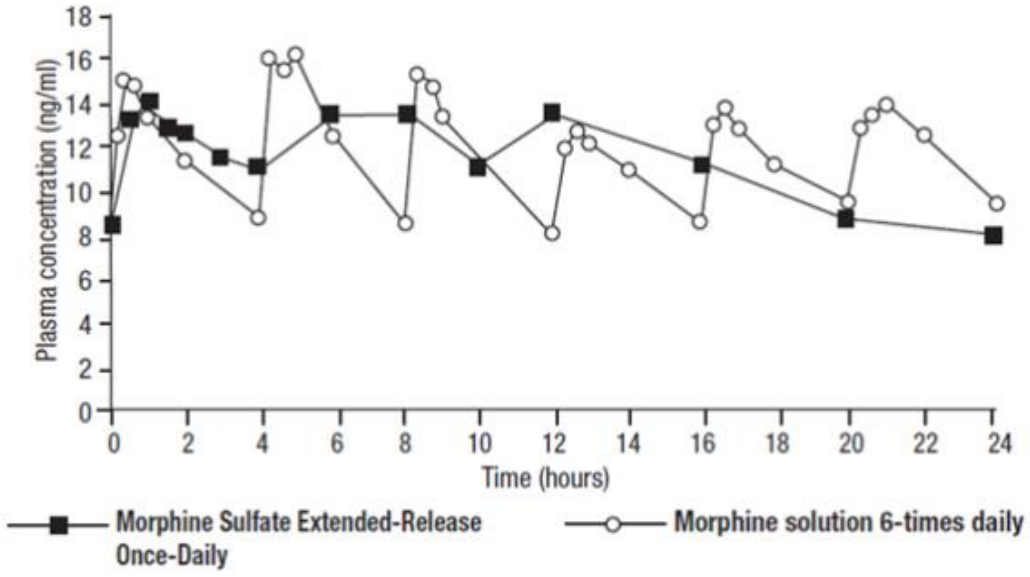
Food Effect: When a 60 mg dose of Morphine Sulfate Extended-Release Capsules was administered immediately following a high fat meal, peak morphine concentrations and AUC values were similar to those observed when the dose of Morphine Sulfate Extended-Release Capsules was administered in a fasting state, although achievement of initial concentrations was delayed by approximately 1 hour under fed conditions. Therefore, Morphine Sulfate Extended-Release Capsules can be administered without regard to food. When the contents of Morphine Sulfate Extended-Release Capsules were administered by sprinkling on applesauce, the rate and extent of morphine absorption were found to be bioequivalent to the same dose when administered as an intact capsule.

Steady State: Steady-state plasma concentrations of morphine are achieved 2 to 3 days after initiation of once-daily administration of Morphine Sulfate Extended-Release Capsules.

Morphine Sulfate Extended-Release 60 mg capsules (once-daily) and 10 mg morphine oral solution (6 times daily) were equally bioavailable.

Graph 1

Mean Steady-State Plasma Morphine Concentrations Following Once-Daily Administration of Morphine Sulfate Extended-Release Capsules or 6-Times Daily Administration of Morphine Solution



A once-daily dose of Morphine Sulfate Extended-Release Capsules provided similar C_{max}, C_{min}, and AUC values and peak-trough fluctuations (% FL, C_{max}-C_{min}/C_{av}) compared to 6-times daily administration of the same total daily dose of morphine oral solution (Table 2).

Table 2 Pharmacokinetic Data Mean ± SD

Parameter	Morphine Sulfate Extended-Release Capsules Once-Daily	Morphine Oral Solution 6-Times Daily
AUC	273.25 ± 81.24	279.11 ± 63.00

(ng/mL.h)	273.23 ± 81.24	279.11 ± 65.00
C_{max} (ng/mL)	18.65 ± 7.13	19.96 ± 4.82
C_{min} (ng/mL)	6.98 ± 2.44	6.61 ±2.15
% FL	106.38 ± 78.14	116.22 ± 26.67

Distribution

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Although the primary site of action is the CNS, only small quantities cross the blood-brain barrier. Morphine also crosses the placental membranes and has been found in breast milk *[see Use in Specific Populations (8.1, 8.3)]*. The volume of distribution of morphine is approximately 1 to 6 L/kg, and morphine is 20 to 35% reversibly bound to plasma proteins.

Elimination

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
Approximately 10% of a morphine dose is excreted unchanged in the urine. Elimination of morphine is primarily via hepatic metabolism to glucuronide metabolites 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 recycling. 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 single dose of Morphine Sulfate Extended-Release Capsules administration is approximately 24 hrs.

Specific Populations

Sex
An analysis of pharmacokinetic data from healthy subjects taking Morphine Sulfate Extended-Release Capsules indicated that morphine concentrations were similar in males and females.

Race/Ethnicity
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.

Drug Interaction/Alcohol Interaction
In *in vitro* studies of the dissolution of Morphine Sulfate Extended-Release Capsules 30 mg mixed with 900 mL of buffer solutions containing ethanol (20% and 40%), the amount of morphine released increased in an alcohol concentration-dependent manner. While the relevance of *in vitro* lab tests regarding Morphine Sulfate Extended-Release Capsules to the clinical setting remains to be determined, this acceleration of release may correlate with *in vivo* rapid release of the total morphine dose, which could result in the absorption of a potentially fatal dose of morphine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies have not been completed to evaluate the carcinogenic potential of morphine.

Mutagenesis

No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the above positive findings, *in vitro* studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*.

Impairment of Fertility

No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies and higher incidence of pseudopregnancies at 20 mg/kg/day (3.2 times the HDD) were reported. Studies from the literature have also reported changes in hormonal levels in male rats (i.e. testosterone, luteinizing hormone) following treatment with morphine at 10 mg/kg/day or greater (1.6 times the HDD).

Female rats that were administered morphine sulfate intraperitoneally prior to mating exhibited prolonged estrous cycles at 10 mg/kg/day (1.6 times the HDD).

Exposure of adolescent male rats to morphine has been associated with delayed sexual maturation, and following mating to untreated females, smaller litters, increased pup mortality, and/or changes in reproductive endocrine status in adult male offspring have been reported (estimated 5 times the plasma levels at the HDD).

14 CLINICAL STUDIES

Morphine Sulfate Extended-Release Capsules were studied in a double-blind, placebo-controlled, fixed-dose, parallel group trial in 295 patients with moderate to severe pain

due to osteoarthritis. These patients had either a prior sub-optimal response to acetaminophen, NSAID therapy, or previously received intermittent opioid analgesic therapy. Thirty-milligrams Morphine Sulfate Extended-Release Capsules administered once-daily, either in the morning or the evening, were more effective than placebo in reducing pain.

Table 3 Change from Baseline in WOMAC OA Index Pain VAS Subscale Score

Overall	Placebo	Morphine Sulfate Extended-Release Capsules QAM	Morphine Sulfate Extended-Release Capsules QPM
LS Mean	-36.23	-75.26[a]	-75.39[a]
Std. Error	11.482	11.305	11.747

a) P<0.05; REPEATED MEASURES ANALYSIS

This study was not designed to assess the effects of Morphine Sulfate Extended-Release Capsules on the course of the osteoarthritis.

16 HOW SUPPLIED/STORAGE AND HANDLING

Morphine Sulfate Extended-Release Capsules, USP (Once Daily) are available as follows:

30 mg – Size 3 capsule with dark blue opaque cap and body, printed with and 3090 on both the cap and body in black ink. Capsules are supplied in bottles of 100 (NDC 0228-3090-11).

45 mg – Size 3 capsule with violet opaque cap and body, printed with and 3116 on both the cap and body in black ink. Capsules are supplied in bottles of 100 (NDC 0228-3116-11).

60 mg – Size 2 capsule with light green opaque cap and body, printed with and 3091 on both the cap and body in black ink. Capsules are supplied in bottles of 100 (NDC 0228-3091-11).

75 mg – Size 1 capsule with brown opaque cap and body, printed with and 3117 on both the cap and body in black ink. Capsules are supplied in bottles of 100 (NDC 0228-3117-11).

90 mg – Size 1 capsule with green opaque cap and body, printed with and 3092 on both the cap and body in black ink. Capsules are supplied in bottles of 100 (NDC 0228-3092-11).

120 mg – Size 0 capsule with light blue opaque cap and body, printed with and 3093 on both the cap and body in black ink. Capsules are supplied in bottles of 100 (NDC 0228-3093-11).

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

Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in USP.

Store Morphine Sulfate Extended-Release Capsules securely and dispose of properly *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store Morphine Sulfate Extended-Release Capsules securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home *[see Warnings and Precautions (5.1, 5.2), Abuse (9.2*)]. Inform patients that leaving Morphine Sulfate Extended-Release Capsules unsecured can pose a deadly risk to others in the home.

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

Addiction, Abuse, and Misuse

Inform patients that the use of Morphine Sulfate Extended-Release Capsules, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share Morphine Sulfate 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.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.3)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with Morphine Sulfate Extended-Release Capsules. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)].*

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone’s effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]*.

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Accidental Ingestion

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

Interactions with Benzodiazepines and Other CNS Depressants

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.

Inform patients and caregivers that potentially fatal additive effects may occur if Morphine Sulfate Extended-Release Capsules are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

Serotonin Syndrome

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

MAOI Interaction

Inform patients not to take Morphine Sulfate Extended-Release Capsules while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking Morphine Sulfate Extended-Release Capsules *[see Warnings and Precautions (5.7)]*.

Adrenal Insufficiency

Inform patients that Morphine Sulfate Extended-Release Capsules could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.8)]*.

Important Administration Instructions

Instruct patients how to properly take Morphine Sulfate Extended-Release Capsules, including the following:

- Swallowing Morphine Sulfate Extended-Release Capsules whole or sprinkling the capsule contents on applesauce and then swallowing immediately without chewing *[see Dosage and Administration (2.1, 2.5)]*
- Not crushing, chewing, or dissolving the pellets in the capsules *[see Dosage and Administration (2.1)]*
- Using Morphine Sulfate Extended-Release Capsules exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) *[see Warnings and Precautions (5.3)]*
- Not discontinuing Morphine Sulfate Extended-Release Capsules without first discussing the need for a tapering regimen with the prescriber *[see Dosage and Administration (2.4)]*

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue Morphine Sulfate Extended-Release Capsules without first discussing a tapering plan

with the prescriber *[see Dosage and Administration (2.4)]*

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) *[see Warnings and Precautions (5.9)]*.

Anaphylaxis

Inform patients that 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 *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

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 (5.4), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that Morphine Sulfate Extended-Release Capsules can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with Morphine Sulfate Extended-Release Capsules *[see Use in Specific Populations (8.2)]*

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.

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 *[see Warnings and Precautions (5.14)]*.

Constipation

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

DEA Order Form Required.

Dispense with Medication Guide available at: www.tevausa.com/medguides

Manufactured For:
Teva Pharmaceuticals
Parsippany, NJ 07054

Rev. H 8/2021

Dispense with Medication Guide available at: www.tevausa.com/medguides

MEDICATION GUIDE
Morphine Sulfate (mor' feen sul' fate) Extended-Release Capsules, USP (Once Daily), 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 or call 911 right away if you take too many 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. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking Morphine Sulfate Extended-Release Capsules with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your Morphine Sulfate Extended-Release Capsules. They could die from taking it. Selling or giving away Morphine Sulfate Extended-Release Capsules is against the law.
- Store Morphine Sulfate Extended-Release Capsules securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

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
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, 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.** Not recommended during treatment with Morphine Sulfate Extended-Release Capsules. It may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- 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. Use the lowest does possible for the shortest time needed.
- Take your prescribed dose every 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 the next day.
- 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.
- 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.**
- Dispose of expired, unwanted, or unused Morphine Sulfate Extended-Release Capsules by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking Morphine Sulfate Extended-Release Capsules DO NOT:
- Drive or operate heavy machinery, until you know how Morphine Sulfate Extended-Release Capsules affect you. Morphine Sulfate Extended-Release Capsules can make you sleepy, dizzy, or lightheaded.
- Drink alcohol, or use prescription or over-the-counter medicines containing alcohol. Using products containing alcohol during treatment with Morphine Sulfate Extended-Release Capsules may cause you to overdose and die.

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

For additional product information about Morphine Sulfate Extended-Release Capsules, contact Teva at 1-888-838-2872.

Manufactured For:
Teva Pharmaceuticals
Parsippany, NJ 07054

Rev. C 8/2021

INSTRUCTIONS FOR USE

Morphine Sulfate (mor' feen sul' fate)
Extended-Release Capsules, USP (Once Daily) CII
- 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:

Open the Morphine Sulfate

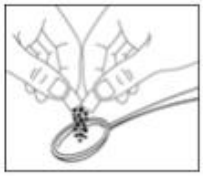


Figure 1

Open the Morphine Sulfate Extended-Release Capsule and sprinkle the pellets over approximately one tablespoon of applesauce *(See Figure 1).*

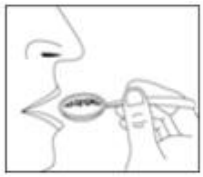


Figure 2

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

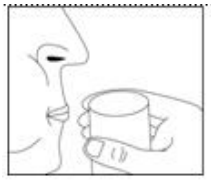


Figure 3

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 or gastric tube (stomach tube).

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured For:
Teva Pharmaceuticals
Parsippany, NJ 07054

Rev. B 8/2021

PRINCIPAL DISPLAY PANEL

NDC 0228-3090-11

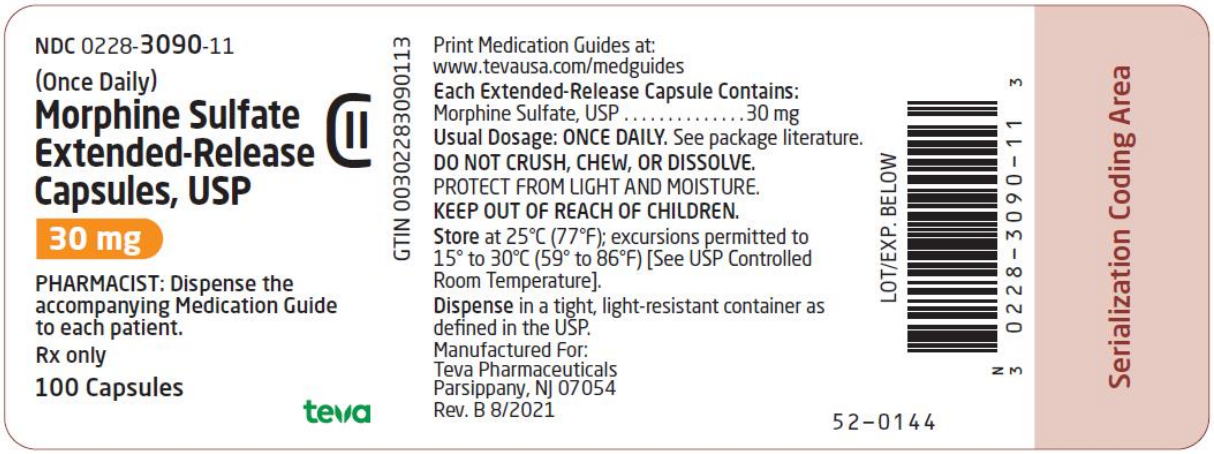
CII

(Once Daily)
Morphine Sulfate Extended-Release Capsules, USP 30 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

100 Capsules



PRINCIPAL DISPLAY PANEL

NDC 0228-3116-11

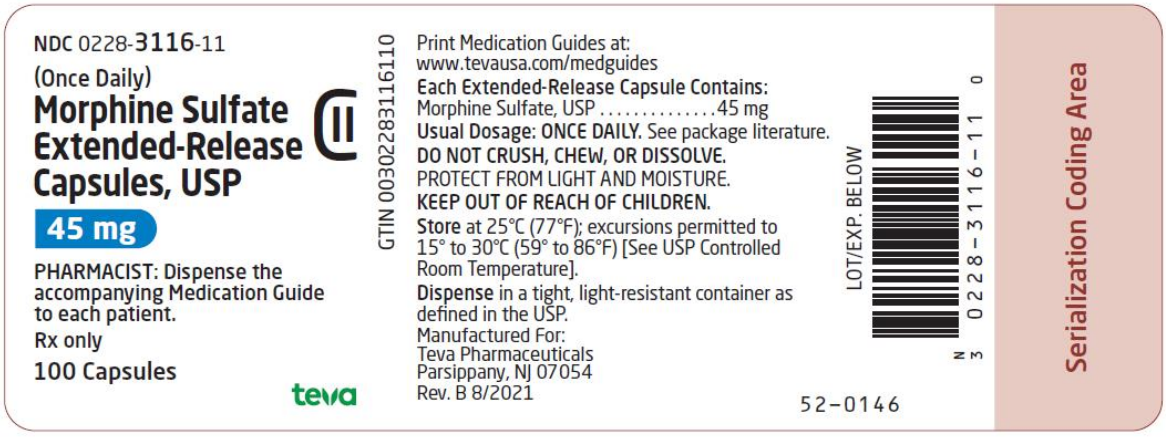
CII

(Once Daily)
Morphine Sulfate Extended-Release Capsules, USP 45 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

100 Capsules



PRINCIPAL DISPLAY PANEL

NDC 0228-3091-11

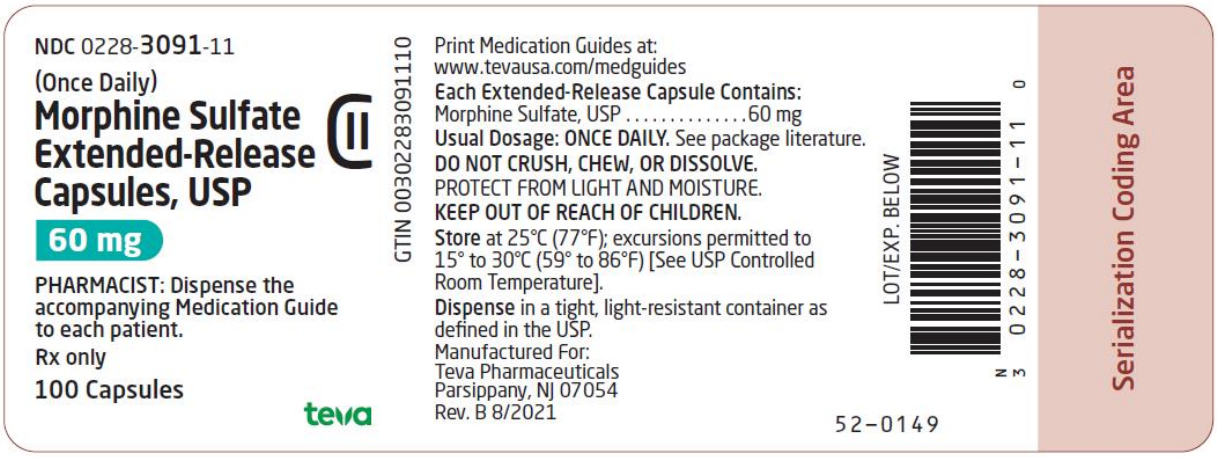
CII

(Once Daily)
Morphine Sulfate Extended-Release Capsules, USP 60 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

100 Capsules



PRINCIPAL DISPLAY PANEL

NDC 0228-3117-11

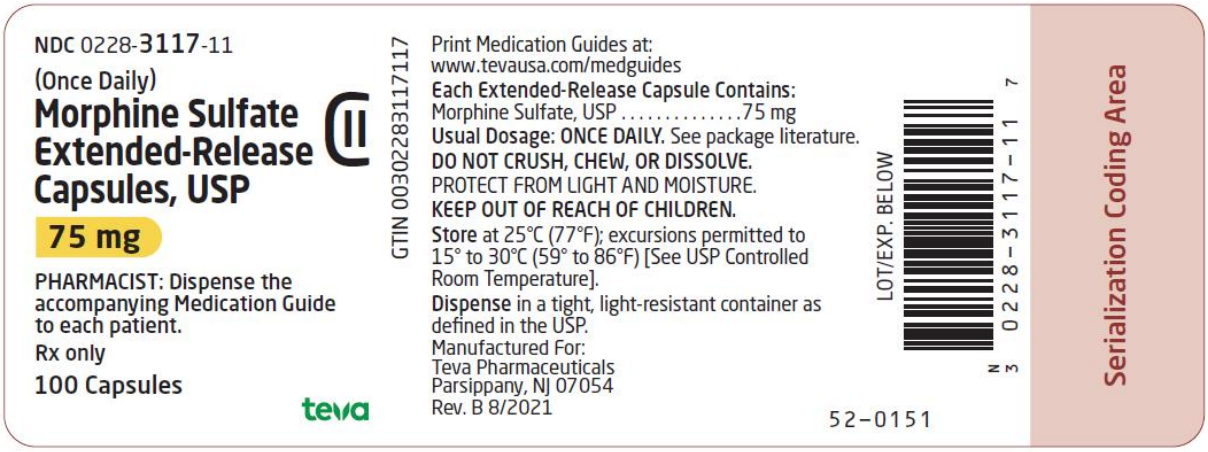
CII

(Once Daily)
Morphine Sulfate Extended-Release Capsules, USP 75 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Rx only

100 Capsules



PRINCIPAL DISPLAY PANEL

NDC 0228-3092-11

Rx only

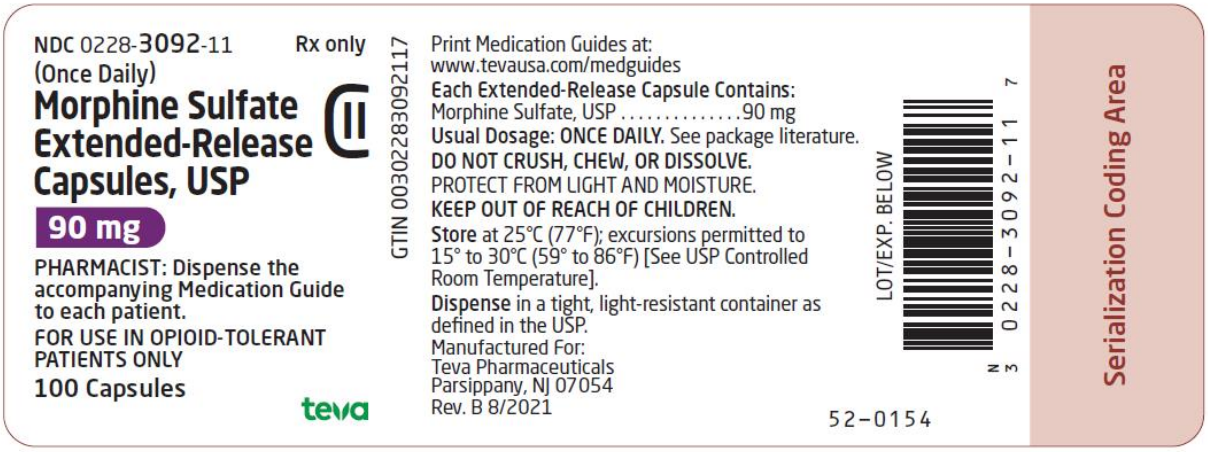
CII

(Once Daily)
Morphine Sulfate Extended-Release Capsules, USP 90 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

100 Capsules



PRINCIPAL DISPLAY PANEL

NDC 0228-3093-11

Rx only

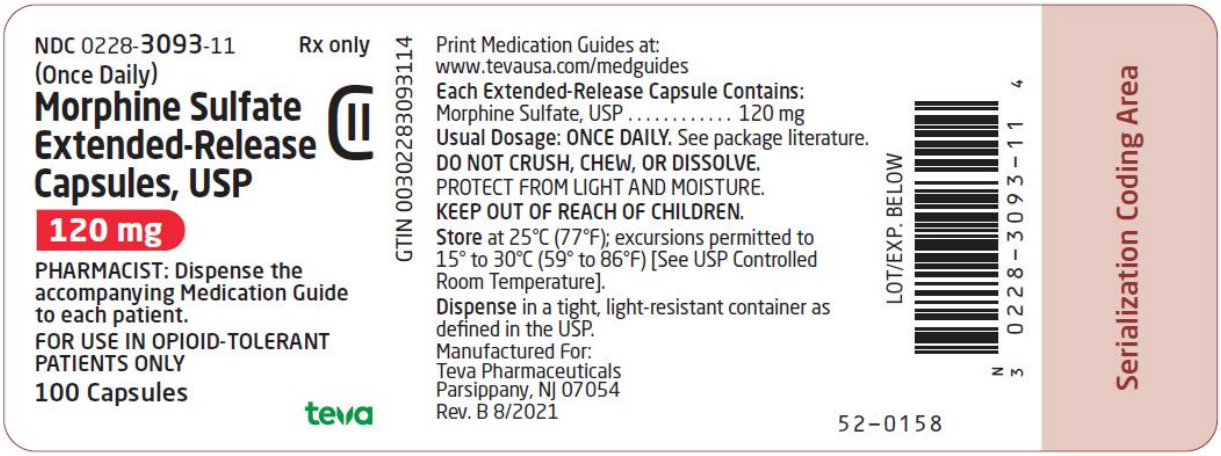
CII

(Once Daily)
Morphine Sulfate Extended-Release Capsules, USP 120 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

100 Capsules



MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-3116
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	45 mg

Inactive Ingredients	
Ingredient Name	**Strength**
DIETHYL PHTHALATE (UNII: UF064M00AF)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
GELATIN (UNII: 2G86QN327L)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1) (UNII: 74G4R6TH13)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics			
Color	purple (Violet)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	3116
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0228-3116-11	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/04/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079040	02/04/2014	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-3091
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**
DIETHYL PHTHALATE (UNII: UF064M00AF)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
GELATIN (UNII: 2G86QN327L)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1) (UNII: 74G4R6TH13)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C GREEN NO. 3 (UNII: 3P3ONR6O1S)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics			
Color	green (Light Green)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	3091
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0228-3091-11	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/04/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079040	02/04/2014	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-3117
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	75 mg

Inactive Ingredients

Ingredient Name	Strength
DIETHYL PHTHALATE (UNII: UF064M00AF)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
GELATIN (UNII: 2G86QN327L)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1) (UNII: 74G4R6TH13)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	brown	**Score**	no score
Shape	CAPSULE	**Size**	20mm
Flavor		**Imprint Code**	3117
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0228-3117-11	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/04/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079040	02/04/2014	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-3092
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	90 mg

Inactive Ingredients

Ingredient Name	Strength
DIETHYL PHTHALATE (UNII: UF064M00AF)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
GELATIN (UNII: 2G86QN327L)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1) (UNII: 74G4R6TH13)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	green	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	3092
Contains			

Packaging

			Marketing Start	Marketing End

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0228-3092-11	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/04/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079040	02/04/2014	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-3093
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	120 mg

Inactive Ingredients

Ingredient Name	Strength
DIETHYL PHTHALATE (UNII: UF064M00AF)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
GELATIN (UNII: 2G86QN327L)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1) (UNII: 74G4R6TH13)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	blue (Light Blue)	**Score**	no score
Shape	CAPSULE	**Size**	23mm
Flavor		**Imprint Code**	3093
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0228-3093-11	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/04/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079040	02/04/2014	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0228-3090
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	30 mg

Inactive Ingredients	
Ingredient Name	Strength
DIETHYL PHTHALATE (UNII: UF064M00AF)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
GELATIN (UNII: 2G86QN327L)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1) (UNII: 74G4R6TH13)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics			
Color	blue (Dark Blue)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	3090

Contains	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0228-3090-11	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/04/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079040	02/04/2014	

Labeler - Actavis Pharma, Inc. (119723554)

Revised: 8/2021 Actavis Pharma, Inc.