MORPHINE SULFATE- morphine sulfate capsule, extended release
Amneal Pharmaceuticals of New York LLC

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
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 OR 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)**

RECENT MAJOR CHANGES

Dosage and Administration (2.4)	10/2019
Warnings and Precautions (5.3, 5.13)	09/2018

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: (1)

- 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 (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.

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 100 mg capsules, a single dose greater than 60 mg, or a total daily dose greater than

120 mg, are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)

- 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)
- Instruct patients to swallow morphine sulfate extended-release capsules intact, or to sprinkle the capsule contents on applesauce and immediately swallow without chewing. (2.1, 2.5)
- Instruct patients not to cut, break, chew, crush, or dissolve the pellets in morphine sulfate extended-release capsules to avoid the risk of release and absorption of potentially fatal dose of morphine. (2.1, 2.5, 5.1)
- For opioid-naïve patients, initiate treatment using an immediate-release morphine formulation and then convert patients to morphine sulfate extended-release capsules. For opioid non-tolerant patients, initiate with a 30 mg capsule orally every 24 hours. Dosage adjustments may be made every one to two days. (2.2, 2.3)
- 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. (2.4, 5.13)

DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg and 100 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, or 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 the opioid. (5.8)
- Severe Hypotension: Monitor during dosage 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 (> 10%): constipation, nausea, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 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)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate effects of morphine. Avoid concomitant use in patients taking MAOIs or within 14 days of stopping treatment with an MAOI. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with morphine sulfate extended-release capsules because they may reduce analgesic effect of morphine sulfate extended-release capsules or precipitate withdrawal symptoms. (5.12, 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: 1/2020

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 OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

Morphine sulfate extended-release capsules expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing morphine sulfate 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 nonprescription products that contain alcohol while taking morphine sulfate extended-release capsules. The co-ingestion of alcohol with morphine sulfate extended-release

capsules may result in increased plasma levels and a potentially fatal overdose of morphine *[see Warnings and Precautions (5.5)]*.

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 injection 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 capsules 100 mg, a single dose greater than 60 mg, or a total daily dose greater than 120 mg, 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 daily, 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 orally at a frequency of either once daily (every 24 hours) or twice daily (every 12 hours).

2.2 Initial Dosage

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

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

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

The starting dose for patients who are not opioid tolerant is morphine sulfate extended-release capsules 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 one-half of the patient's total daily oral morphine dose as morphine sulfate extended-release capsules twice daily or by administering the total daily oral morphine dose as morphine sulfate extended-release capsules once daily. There are no data to support the efficacy or safety of prescribing morphine sulfate extended-release capsules more frequently than every 12 hours.

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

as needed.

Conversion from Parenteral Morphine, or Other Opioids to Morphine Sulfate Extended-Release Capsules

When converting from parenteral morphine or other non-morphine opioids (parenteral or oral) to morphine sulfate extended-release capsules, consider the following general points:

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

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

Conversion from Methadone to Morphine Sulfate Extended-Release Capsules

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

2.3 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 the use of opioid analgesics.

Patients who experience breakthrough pain may require a dosage adjustment 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. In patients experiencing inadequate analgesia with once daily dosing of morphine sulfate extended-release capsules, consider a twice daily regimen. Because steady-state plasma concentrations are approximated within 24 to 36 hours, morphine sulfate extended-release capsules dosage adjustments may be done every 1 to 2 days.

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

2.4 Safe Reduction or Discontinuation of Morphine Sulfate 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 comorbid 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)]*.

2.5 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.

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

1. Flush the gastrostomy tube with water to ensure that it is wet.
2. Sprinkle the morphine sulfate extended-release capsules pellets into 10 mL of water.
3. Use a swirling motion to pour the pellets and water into the gastrostomy tube through a funnel.

4. Rinse the beaker with a further 10 mL of water and pour this into the funnel.
5. Repeat rinsing until no pellets remain in the beaker.

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

3 DOSAGE FORMS AND STRENGTHS

Morphine sulfate extended-release capsules, USP contains white to off-white polymer-coated extended-release pellets of morphine sulfate, USP, have an outer opaque capsule with colors and imprints as identified below, and are available in seven dose strengths.

Morphine Sulfate Extended-Release Capsules USP, 20 mg, has a yellow opaque body and cap, imprinted with “J62” in black ink on cap.

Morphine Sulfate Extended-Release Capsules USP, 30 mg, has a violet opaque body and cap, imprinted with “J63” in black ink on cap.

Morphine Sulfate Extended-Release Capsules USP, 40 mg, has a blue violet opaque body and rich yellow opaque cap, imprinted with “J69” in black ink on cap.

Morphine Sulfate Extended-Release Capsules USP, 50 mg, has a light blue opaque body and cap, imprinted with “J64” in black ink on cap.

Morphine Sulfate Extended-Release Capsules USP, 60 mg, has a red opaque body and cap, imprinted with “J65” in black ink on cap.

Morphine Sulfate Extended-Release Capsules USP, 80 mg, has an orange opaque body and cap, imprinted with “J66” in black ink on cap.

Morphine Sulfate Extended-Release Capsules USP, 100 mg, has a light green opaque body and cap, imprinted with “J67” in black ink on cap.

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), Drug Interactions (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 contains morphine, a Schedule II controlled substance. As an opioid, morphine sulfate extended-release capsules expose 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 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.

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

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 Healthcare 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 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[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 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 dosage 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.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.4)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of morphine sulfate extended-release capsules during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.5 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

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

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)]*.

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.

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 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 dosage 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 morphine in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.4), Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist analgesics (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 agonists/antagonists 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 Benzodiazepine or Other CNS Depressants *[see Warnings and Precautions (5.5)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.8)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*

- Withdrawal *[see Warnings and Precautions (5.13)]*

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

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

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

release capsules or seen in less than 2% of patients in the clinical trials were:

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

Four-Week Open-Label Safety Study

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

6.2 Post-Marketing Experience

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 Warnings and Precautions (5.5)]*.
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.3)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue morphine sulfate 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-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.7)]*.
	Do not use morphine sulfate extended-release capsules in

Intervention:	patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of morphine sulfate 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.
Cimetidine	
Clinical Impact:	The concomitant use of cimetidine can potentiate morphine effects and 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 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 can 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 sulfate extended-release capsules 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 Nonclinical Toxicology (13)]*.

8.4 Pediatric Use

The safety and efficacy of morphine sulfate extended-release capsules in patients less than 18 years have not been established.

8.5 Geriatric Use

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

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)]*.

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

8.6 Hepatic Impairment

Morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Start these patients with a lower than usual dosage of morphine sulfate 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 usual 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, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of 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 over dose and death.

Due to the presence of talc as one of the excipients in morphine sulfate extended-release capsules, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, 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), Warnings and Precautions (5.13)]*.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.2), Warnings and Precautions (5.4)]*.

10 OVERDOSAGE

Clinical Presentation

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

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 and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

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

Because the duration of 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 add to the morphine load for 24 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 in the product's prescribing information.

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

11 DESCRIPTION

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

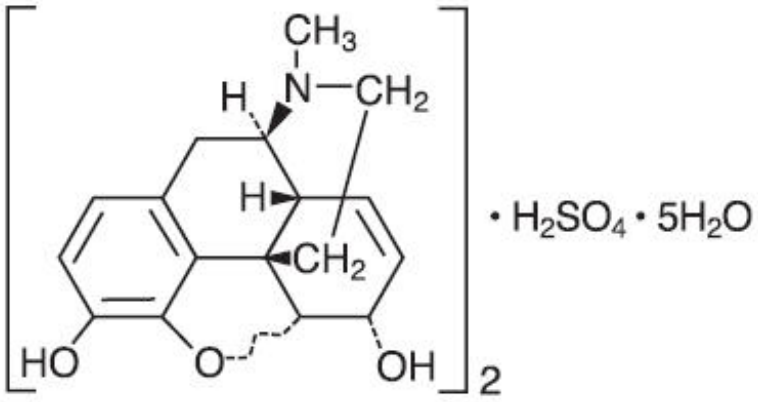
Each morphine sulfate extended-release capsule, USP contains either 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg, or 100 mg of morphine sulfate, USP and the following inactive ingredients common to all

strengths: hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, corn starch, and sucrose.

The capsule shells contain gelatin and titanium dioxide. In addition, the 20 mg and 40 mg capsule shells contain yellow iron oxide; the 30 mg and 40 mg capsule shells contain FD&C Blue No. 1 and FD&C Red No. 3; the 50 mg capsule shell contains FD&C Blue No. 1; the 60 mg capsule shell contains FD&C Red No. 40; the 80 mg capsule shell contains D&C Red No. 28, D&C Yellow No. 10, and FD&C Red No. 40; and the 100 mg capsule shell contains D&C Yellow No. 10 and FD&C Green No. 3. The black ink contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide, and purified water.

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

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



USP dissolution test pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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 associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Morphine produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release 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 androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

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

Concentration-Efficacy Relationships

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

Concentration–Adverse Reaction Relationships

There is a relationship between increasing morphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

12.3 Pharmacokinetics

Absorption

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

40% of the administered dose reaches the systemic circulation.

Both dose-normalized C_{max} and dose-normalized AUC_{0-48hr} values of morphine after a single dose administration of morphine sulfate extended-release capsules in healthy volunteers are less than those for morphine oral solution or an extended-release tablet formulation (Table 2).

When morphine sulfate extended-release capsules were given twice daily to 24 patients with chronic pain due to malignancy, steady-state was achieved in about two days. At steady-state, morphine sulfate extended-release capsules have a significantly lower C_{max} and a higher C_{min} than equivalent doses of oral morphine solution given every 4 hours and an extended-release tablet given twice daily. When given once daily to 24 patients with malignancy, morphine sulfate extended-release capsules had a similar C_{max} and higher C_{min} at steady-state when compared to extended-release morphine tablets, given twice daily at an equivalent total daily dosage (see Table 2).

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

Table 2: Mean pharmacokinetic parameters (% coefficient variation) resulting from a fasting single dose study in normal volunteers and a multiple-dose study in patients with cancer pain

Regimen/Dosage Form	**AUC[#, +] (ng·h/mL)**	**C_{max}[+] (ng/mL)**	**T_{max} (h)**	**C_{min}[+] (ng/mL)**	**Fluctuation[*]**
Single Dose (n=24)					
Morphine Sulfate Extended-Release Capsule	271.0 (19.4)	15.6 (24.4)	8.6 (41.1)	N/A	N/A
Extended-Release Tablet	304.3 (19.1)	30.5 (32.1)	2.5 (52.6)	N/A	N/A
Morphine Solution	362.4 (42.6)	64.4 (38.2)	0.9 (55.8)	N/A	N/A
Multiple Dose (n=24)					
Morphine Sulfate Extended-Release Capsule Once Daily	500.9 (38.6)	37.3 (37.7)	10.3 (32.2)	9.9 (52.3)	3.0 (45.5)
Extended-Release Tablet Twice Daily	457.3 (40.2)	36.9 (42.0)	4.4 (53.0)	7.6 (60.3)	4.1 (51.5)

[#] For single dose AUC = AUC_{0-48h}, for multiple dose AUC = AUC_{0-24h} at steady-state
[+] For single dose parameter normalized to 100 mg, for multiple dose parameter normalized to 100 mg per 24 hours
[*] Steady-state fluctuation in plasma concentrations = C_{max}-$C_{min/Cmin}$

Food Effect

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

Distribution

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. The volume of distribution of morphine is approximately 3 to 4 L/kg. Morphine is 30% to 35% reversibly bound to plasma proteins. Although the primary site of action of morphine is in the CNS, only small quantities pass the blood-brain barrier. Morphine also crosses the placental membranes *[see Use in Specific Populations (8.1)]* and has been found in breast milk *[see Use in Specific Populations (8.4)]*.

Elimination

Metabolism

Major pathways of morphine metabolism include glucuronidation in the liver to produce metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5% to 15%) and sulfation in the liver to produce morphine-3-etheral sulfate. A small fraction (less than 5%) of morphine is demethylated. M3G has no significant contribution to the analgesic activity. Although M6G does not readily cross the blood-brain barrier, it has been shown to have opioid agonist and analgesic activity in humans.

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

Excretion

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

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

Specific Populations

Sex

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

Race/Ethnicity

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

Hepatic Impairment

Morphine pharmacokinetics are altered in patients with alcoholic cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine AUC ratios also decreased in these patients, indicating a decrease in metabolic activity. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted.

Renal Impairment

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

Mutagenesis

No formal studies to assess the mutagenic potential of morphine have been conducted. In the published

literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the above positive findings, *in vitro* studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*.

Impairment of Fertility

No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies and higher incidence of pseudo pregnancies at 20 mg/kg/day (3.2 times the HDD) were reported.

Studies from the literature have also reported changes in hormonal levels in male rats (i.e. testosterone, luteinizing hormone) following treatment with morphine at 10 mg/kg/day or greater (1.6 times the HDD).

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Morphine sulfate extended-release capsules, USP contain white to off-white polymer-coated extended-release pellets of morphine sulfate and are available in seven dose strengths.

Morphine Sulfate Extended-Release Capsules USP, **20 mg** are size 4 capsule, yellow opaque body and cap, imprinted with “J62” in black ink on cap.
Capsules are supplied as follows:

Bottles of 30:	NDC 0115-1277-08
Bottles of 60:	NDC 0115-1277-13
Bottles of 100:	NDC 0115-1277-01
Bottles of 1000:	NDC 0115-1277-03

Morphine Sulfate Extended-Release Capsules USP, **30 mg** are size 4 capsule, violet opaque body and cap, imprinted with “J63” in black ink on cap.
Capsules are supplied as follows:

Bottles of 30:	NDC 0115-1278-08
Bottles of 60:	NDC 0115-1278-13
Bottles of 100:	NDC 0115-1278-01
Bottles of 1000:	NDC 0115-1278-03

Morphine Sulfate Extended-Release Capsules USP, **40 mg** are size 2 capsule, blue violet opaque body and rich yellow opaque cap, imprinted with “J69” in black ink on cap.
Capsules are supplied as follows:

Bottles of 100:	NDC 0115-1479-01

Morphine Sulfate Extended-Release Capsules USP, **50 mg** are size 2 capsule, light blue opaque body

and cap, imprinted with “J64” in black ink on cap.
Capsules are supplied as follows:

Bottles of 30:	NDC 0115-1279-08
Bottles of 60:	NDC 0115-1279-13
Bottles of 100:	NDC 0115-1279-01
Bottles of 1000:	NDC 0115-1279-03

Morphine Sulfate Extended-Release Capsules USP, **60 mg** are size 1 capsule, red opaque body and cap, imprinted with “J65” in black ink on cap.
Capsules are supplied as follows:

Bottles of 30:	NDC 0115-1280-08
Bottles of 60:	NDC 0115-1280-13
Bottles of 100:	NDC 0115-1280-01
Bottles of 1000:	NDC 0115-1280-03

Morphine Sulfate Extended-Release Capsules USP, **80 mg** are size 0 capsule, orange opaque body and cap, imprinted with “J66” in black ink on cap.
Capsules are supplied as follows:

Bottles of 30:	NDC 0115-1281-08
Bottles of 60:	NDC 0115-1281-13
Bottles of 100:	NDC 0115-1281-01
Bottles of 1000:	NDC 0115-1281-03

Morphine Sulfate Extended-Release Capsules USP, **100 mg** are size 0 capsule, light green opaque body and cap, imprinted with “J67” in black ink on cap.
Capsules are supplied as follows:

Bottles of 30:	NDC 0115-1282-08
Bottles of 60:	NDC 0115-1282-13
Bottles of 100:	NDC 0115-1282-01
Bottles of 1000:	NDC 0115-1282-03

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light and moisture. Dispense in a tightly-closed, light-resistant container as defined in the USP, with a child-resistant closure, as required.

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, 5.3), Drug Abuse and Dependence (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 dosage is increased, and that it can occur even at recommended doses *[see Warnings and Precautions (5.3)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

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

Interactions with Alcohol

Instruct patients not to consume alcoholic beverages, or prescription and non-prescription products that contain alcohol, during treatment with morphine sulfate extended-release capsules. The co-ingestion of alcohol with morphine sulfate extended-release capsules may result in increased plasma levels and a potentially fatal overdose of morphine *[see Drug Interactions (7)]*.

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 (active opioid) *[see Warnings and Precautions (5.5)]*.

Serotonin Syndrome

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

MAOI Interaction

Inform patients not to take morphine sulfate 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), Drug Interactions (7)]*.

Adrenal Insufficiency

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

Important Administration Instructions

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

- Swallow morphine sulfate extended-release capsules whole or sprinkling the capsule contents on applesauce and then swallow immediately without chewing *[see Dosage and Administration (2.1,*

2.5)].

- Do not crush, chew, or dissolve the pellets contained in the capsules due to a risk of fatal morphine overdose *[see Dosage and Administration (2.1)]*.
- Use 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)]*.

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 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), Clinical Pharmacology (12.2)]*.

Manufactured by:

Amneal Pharmaceuticals of NY, LLC
Brookhaven, NY 11719

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Bridgewater, NJ 08807

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Medication Guide

MorphineSulfate (mor' feen sul' fate) **Extended-Release Capsules, USP, CII**

Morphine sulfate extended-release capsules are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about morphine sulfate extended-release capsules:

- **Get emergency help right away if you take too much morphine sulfate extended-release capsules (overdose).** When you first start taking morphine sulfate extended-release capsules, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- 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, 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.

- 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 dose possible for the shortest time needed.
- Take your prescribed dose every 12 or 24 hours at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time.
- Swallow morphine sulfate extended-release capsules whole. Do not cut, break, chew, crush, dissolve, snort, or inject morphine sulfate extended-release capsules because this may cause you to overdose and die.
- You should not receive morphine sulfate extended-release capsules through a nasogastric tube.
- If you cannot swallow morphine sulfate extended-release capsules, see the detailed Instructions for Use.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking morphine sulfate extended-release capsules without talking to your healthcare provider.**
- 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 that contain alcohol. Using products containing alcohol during treatment with morphine sulfate extended-release capsules may cause you to overdose and die.

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

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

Get emergency medical help if you have:

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

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

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

Manufactured by:
Amneal Pharmaceuticals of NY, LLC
Brookhaven, NY 11719

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Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 11-2019-01

Instructions For Use

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

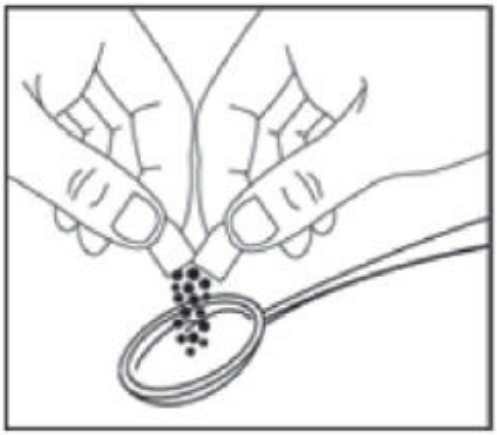


Figure 1

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

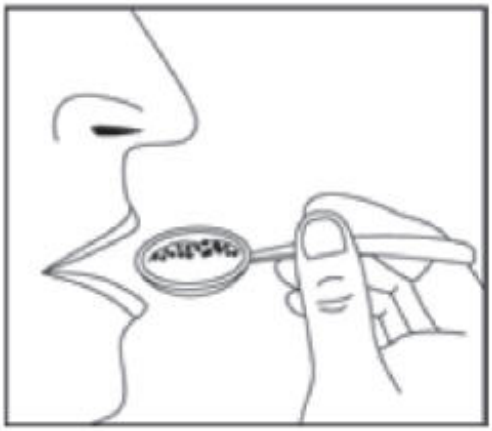


Figure 2

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

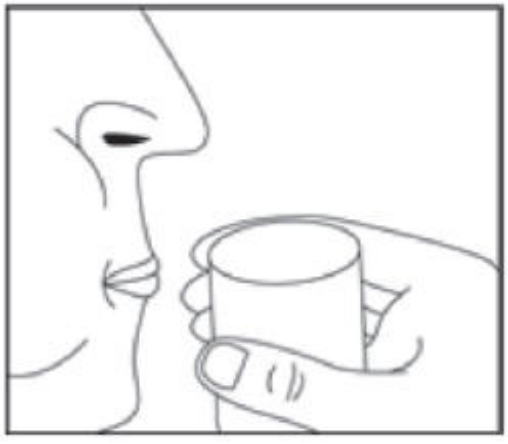


Figure 3

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

Figure 4

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

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

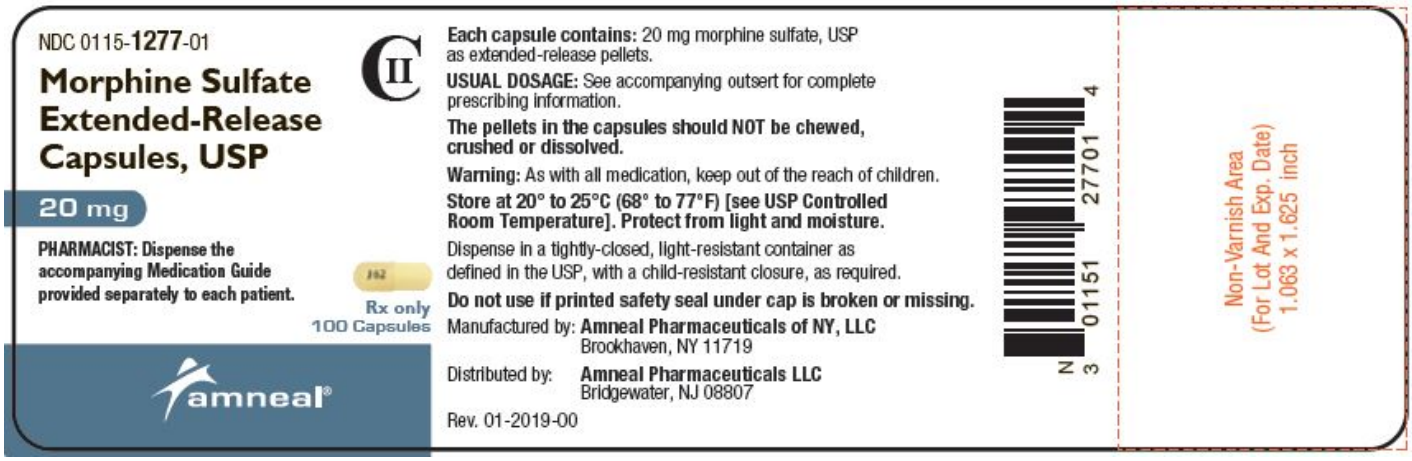
This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Amneal Pharmaceuticals of NY, LLC
Brookhaven, NY 11719

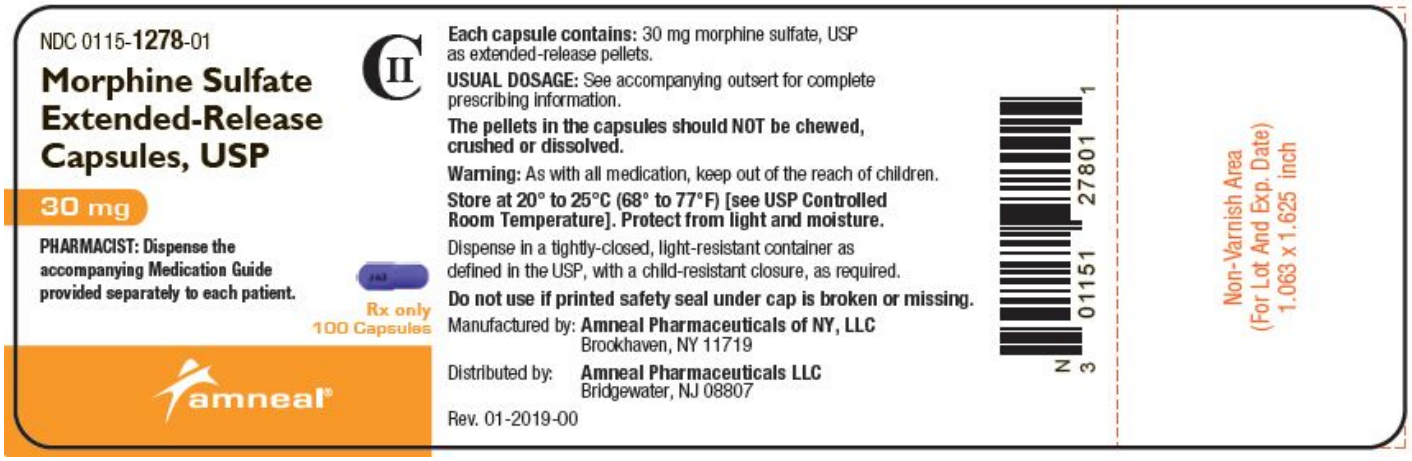
Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 11-2019-01

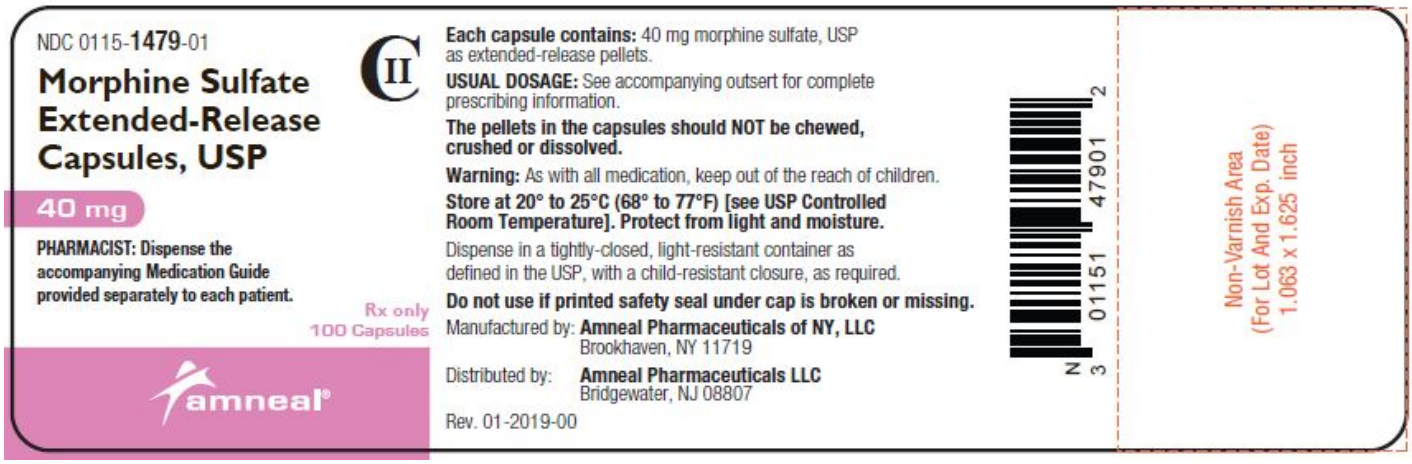
PRINCIPAL DISPLAY PANEL - 20 mg Capsule Bottle Label



PRINCIPAL DISPLAY PANEL - 30 mg Capsule Bottle Label



PRINCIPAL DISPLAY PANEL - 40 mg Capsule Bottle Label



PRINCIPAL DISPLAY PANEL - 50 mg Capsule Bottle Label

PRINCIPAL DISPLAY PANEL - 60 mg Capsule Bottle Label

PRINCIPAL DISPLAY PANEL - 80 mg Capsule Bottle Label

PRINCIPAL DISPLAY PANEL - 100 mg Capsule Bottle Label

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0115-1277
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	20 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
DIETHYL PHTHALATE (UNII: UF064M00AF)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	YELLOW (opaque)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	J62
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1277-08	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
2	NDC:0115-1277-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
3	NDC:0115-1277-03	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200411	04/12/2016	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0115-1278
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**
HYPROMELLOSES (UNII: 3NXW29V3WO)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
DIETHYL PHTHALATE (UNII: UF064M00AF)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics			
Color	PURPLE (violet opaque)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	J63
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1278-08	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
2	NDC:0115-1278-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
3	NDC:0115-1278-03	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200411	04/12/2016	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0115-1279
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	50 mg

Inactive Ingredients	
Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
DIETHYL PHTHALATE (UNII: UF064M00AF)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	

WATER (UNII: 059QF0KO0R)	

Product Characteristics			
Color	BLUE (light blue opaque)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	J64
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1279-08	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
2	NDC:0115-1279-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
3	NDC:0115-1279-03	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200411	04/12/2016	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0115-1280
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
HYPROMELLOSES (UNII: 3NXW29V3WO)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
DIETHYL PHTHALATE (UNII: UF064M00AF)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN (UNII: 2G86QN327L)	

TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	RED (opaque)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	J65
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1280-08	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
2	NDC:0115-1280-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
3	NDC:0115-1280-03	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200411	04/12/2016	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0115-1281
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	80 mg

Inactive Ingredients

Ingredient Name	Strength

HYPROMELLOSES (UNII: 3NXW29V3WO)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
DIETHYL PHTHALATE (UNII: UF064M00AF)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	ORANGE (opaque)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	J66
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1281-08	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
2	NDC:0115-1281-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
3	NDC:0115-1281-03	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200411	04/12/2016	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0115-1282

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	100 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
DIETHYL PHTHALATE (UNII: UF064M00AF)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C GREEN NO. 3 (UNII: 3P3ONR6O1S)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	GREEN (light green opaque)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	J67
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1282-08	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
2	NDC:0115-1282-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	
3	NDC:0115-1282-03	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/12/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200411	04/12/2016	

MORPHINE SULFATE

morphine sulfate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0115-1479
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	40 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
ETHYLCELLULOSES (UNII: 7Z8S9VYZ4B)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
DIETHYL PHTHALATE (UNII: UF064M00AF)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	BLUE (BLUE-VIOLET opaque body) , YELLOW (opaque cap)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	J69

Contains	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1479-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/05/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200411	10/05/2018	

Labeler - Amneal Pharmaceuticals of New York LLC (123797875)

Establishment

Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals of New York, LLC		123797875	ANALYSIS(0115-1277, 0115-1278, 0115-1279, 0115-1280, 0115-1281, 0115-1282, 0115-1479) , LABEL(0115-1277, 0115-1278, 0115-1279, 0115-1280, 0115-1281, 0115-1282, 0115-1479) , MANUFACTURE(0115-1277, 0115-1278, 0115-1279, 0115-1280, 0115-1281, 0115-1282, 0115-1479) , PACK(0115-1277, 0115-1278, 0115-1279, 0115-1280, 0115-1281, 0115-1282, 0115-1479)

Revised: 1/2020 Amneal Pharmaceuticals of New York LLC