HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AVINZA safely and effectively. See full prescribing information for AVINZA.

AVINZA® (morphine sulfate) extended-release capsules, for oral use, CII
Initial U.S. Approval: 1941

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

See full prescribing information for complete boxed warning.

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

----------RECENT MAJOR CHANGES----------

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

----------INDICATIONS AND USAGE----------

AVINZA is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve AVINZA for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.(1)
- AVINZA is not indicated as an as-needed (prn) analgesic. (1)

----------DOSAGE AND ADMINISTRATION----------

- AVINZA 90 mg and 120 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid. (2.1)
- For opioid-naïve and opioid non-tolerant patients, initiate with 30 mg capsules orally every 24 hours. Dose can be increased every 3 to 4 days using increments of 30 mg. (2.1, 2.2)
- Do not abruptly discontinue AVINZA in a physically-dependent patient. (2.3, 5.11)
- Instruct patients to swallow AVINZA capsules intact, or to sprinkle the capsule contents on applesauce and immediately swallow without chewing. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs because of additive pharmacological effects. (5.4, 7.2)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)
- Hypotensive effect: Monitor during dose initiation and titration. (5.7)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of AVINZA in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥10%) are constipation, nausea, somnolence, vomiting and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with AVINZA because they may reduce analgesic effect of AVINZA or precipitate withdrawal symptoms. (5.11, 7.3)
- Monoamine oxidase inhibitors (MAOIs): Avoid AVINZA in patients taking MAOIs or within 14 days of stopping such treatment. (7.5)

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

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

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of AVINZA. Monitor for respiratory depression, especially during initiation of AVINZA or following a dose increase. Instruct patients to swallow AVINZA capsules whole or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing, or dissolving AVINZA can cause rapid release and absorption of a potentially fatal dose of morphine *[see Warnings and Precautions (5.2)]*.

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

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

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

1 INDICATIONS AND USAGE

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

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve AVINZA 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.
- AVINZA is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

AVINZA should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

AVINZA 90 mg and 120 mg capsules are for use only in patients in whom tolerance to an opioid of comparable potency has been established. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with AVINZA *[see Warnings and Precautions (5.2)]*.

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

AVINZA is administered at a frequency of once daily (every 24 hours).

Use of AVINZA as the First Opioid Analgesic
Initiate treatment with AVINZA with 30 mg capsule orally every 24 hours. Adjust the dose of AVINZA in increments not greater than 30 mg every 3 to 4 days.

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

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

Conversion from Other Opioids to AVINZA
There are no established conversion ratios from other opioids to AVINZA defined by clinical trials. Discontinue all other around-the-clock opioid drugs when AVINZA therapy is initiated and initiate dosing using AVINZA 30 mg orally every 24 hours.

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

Conversion from Other Oral Morphine Formulations to AVINZA
Patients receiving other oral morphine formulations may be converted to AVINZA by administering the patient's total daily oral morphine dose as AVINZA once-daily. AVINZA should not be given more frequently than every 24 hours.

Conversion from Parenteral Morphine or Other Non-Morphine Opioids (Parenteral or Oral) to AVINZA
When converting from parenteral morphine or other non-morphine opioids (parenteral or oral) to AVINZA, consider the following general points:

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

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

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

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

2.2 Titration and Maintenance of Therapy

Individually titrate AVINZA to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving AVINZA to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other

members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the AVINZA dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within 2 to 3 days, AVINZA dosage adjustments may be done every 3 to 4 days.

Patients who experience breakthrough pain may require a dose increase of AVINZA, 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 AVINZA dose.

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

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

2.3 Discontinuation of AVINZA

When a patient no longer requires therapy with AVINZA, use a gradual downward titration of the dose every 2 to 4 days, to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue AVINZA.

2.4 Administration of AVINZA

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

Alternatively, the contents of the AVINZA 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 AVINZA capsules after the contents have been sprinkled on applesauce.

Do not administer AVINZA pellets through a nasogastric or gastric tubes.

3 DOSAGE FORMS AND STRENGTHS

AVINZA contains white to off-white color pellets, have an outer opaque capsule with colors as identified below and are available in six dose strengths:

Each 30 mg extended-release capsule has a yellow opaque cap with “AVINZA” printed on it and a white opaque body printed with “30” and “505”.

Each 45 mg extended-release capsule has a light blue opaque cap with “AVINZA” printed on it and a white opaque body printed with “45” and “509”.

Each 60 mg extended-release capsule has a bluish-green opaque cap with “AVINZA” printed on it and a white opaque body printed with “60” and “506”.

Each 75 mg extended-release capsule has an orange opaque cap with “AVINZA” printed on it and a white opaque body printed with “75” and “510”.

Each 90 mg extended-release capsule has a red opaque cap with “AVINZA” printed on it and a white opaque body printed with “90” and “507”.

Each 120 mg extended-release capsule has a blue-violet opaque cap with “AVINZA” printed on it and a white opaque body printed with “120” and “508”.

4 CONTRAINDICATIONS

AVINZA is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (e.g., anaphylaxis) to morphine [*see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

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

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

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing AVINZA, and monitor all patients receiving AVINZA for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of AVINZA for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as AVINZA, but use in such patients necessitates intensive counseling about the risks and proper use of AVINZA along with intensive monitoring for signs of addiction, abuse, and misuse.

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

Opioid agonists such as AVINZA are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing AVINZA. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of AVINZA, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with AVINZA and following dose increases.

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

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

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of AVINZA during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

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

5.4 Interactions with Central Nervous System Depressants

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

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

When considering the use of AVINZA in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin AVINZA is made, start with AVINZA 30 mg every 24 hours, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.2)]*.

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating AVINZA and when AVINZA is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*.

5.6 Use in Patients with Chronic Pulmonary Disease

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

5.7 Hypotensive Effect

AVINZA may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) *[see Drug Interactions (7.2)]*. Monitor these patients for signs of hypotension after initiating or titrating the dose of AVINZA. In patients with circulatory shock, AVINZA may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of AVINZA in patients with circulatory shock.

5.8 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking AVINZA who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with AVINZA. AVINZA may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of AVINZA in patients with impaired consciousness or coma.

5.9 Use in Patients with Gastrointestinal Conditions

AVINZA is contraindicated in patients with paralytic ileus. Avoid the use of AVINZA in patients with other GI obstruction.

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

5.10 Use in Patients with Convulsive or Seizure Disorders

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

5.11 Avoidance of Withdrawal

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

When discontinuing AVINZA, gradually taper the dose *[see Dosage and Administration (2.3)]*. Do not abruptly discontinue AVINZA.

5.12 Driving and Operating Machinery

AVINZA 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 AVINZA and know how they will react to the medication.

6 ADVERSE REACTIONS

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

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

The most common adverse reactions with AVINZA include constipation, nausea and somnolence.

6.1 Clinical Trial Experience

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

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

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

Body as a Whole: malaise, withdrawal syndrome.
Cardiovascular System: bradycardia, hypertension, hypotension, palpitations, syncope, tachycardia.
Digestive System: biliary pain, dyspepsia, dysphagia, gastroenteritis, abnormal liver function tests, rectal disorder, thirst.
Hemic and Lymphatic System: anemia, thrombocytopenia.
Metabolic and Nutritional Disorders: edema, weight loss.
Musculoskeletal: skeletal muscle rigidity.
Nervous System: abnormal dreams, abnormal gait, agitation, amnesia, anxiety, ataxia, confusion, convulsions, coma, delirium, euphoria, hallucinations, lethargy, nervousness, abnormal thinking, tremor, vasodilation, vertigo.
Respiratory System: hiccup, hypoventilation, voice alteration.
Skin and Appendages: dry skin, urticaria.
Special Senses: amblyopia, eye pain, taste perversion.
Urogenital System: abnormal ejaculation, dysuria, impotence, decreased libido, oliguria, urinary retention.

Anaphylaxis has been reported with ingredients contained in AVINZA. Advise patients how to recognize such a reaction and when to seek medical attention.

7 DRUG INTERACTIONS

7.1 Alcohol

Concomitant use of alcohol with AVINZA can result in an increase of morphine plasma levels and potentially fatal overdose of morphine. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on AVINZA therapy *[see Clinical Pharmacology (12.3)]*.

7.2 CNS Depressants

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

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

7.3 Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of AVINZA or may precipitate withdrawal symptoms. Avoid the use of agonist/antagonist and partial agonist analgesics in patients receiving AVINZA.

7.4 Muscle Relaxants

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

7.5 Monoamine Oxidase Inhibitors (MAOIs)

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

7.6 Cimetidine

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

7.7 Diuretics

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

7.8 Anticholinergics

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

7.9 P-Glycoprotein (PGP) Inhibitors

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

.*Teratogenic Effects* - Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. AVINZA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during

pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

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

Nonteratogenic Effects

Infants born to mothers who have taken opioids chronically may exhibit neonatal withdrawal syndrome [see *Warnings and Precautions (5.3)*], reversible reduction in brain volume, small size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

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

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. AVINZA is not for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

8.3 Nursing Mothers

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

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

The pharmacokinetics of AVINZA have not been studied in elderly patients. In clinical studies of AVINZA, 100 patients who received AVINZA were age 65 and over, including 37 patients over the age of 74. No overall differences in safety were observed between these subjects and younger subjects. *[see Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AVINZA contains morphine, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. AVINZA can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1)*].

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

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

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

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

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

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

AVINZA, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state law, is strongly advised.

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

Risks Specific to Abuse of AVINZA
AVINZA is for oral use only. Abuse of AVINZA poses a risk of overdose and death. This risk is increased with concurrent abuse of AVINZA with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved AVINZA enhances drug release and increases the risk of overdose and death.

Due to the presence of talc as one of the excipients in AVINZA, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

AVINZA should not be abruptly discontinued [*see Dosage and Administration (2.3)*]. If AVINZA is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

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

10 OVERDOSAGE

Clinical Presentation

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

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Such agents should be administered cautiously to persons who are known, or suspected to be physically dependent on AVINZA. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Because the duration of reversal would be expected to be less than the duration of action of morphine in AVINZA, carefully monitor the patient until spontaneous respiration is reliably re-established. AVINZA will continue to release morphine and add to the morphine load for 36 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be administered as directed in the product's prescribing information.

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

11 DESCRIPTION

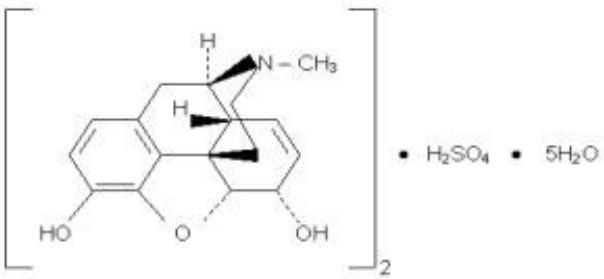
AVINZA extended-release capsules are for oral use and contain pellets of morphine sulfate. Morphine sulfate is an agonist at the mu-opioid receptor.

Each AVINZA extended-release capsule contains either 30, 45, 60, 75, 90, or 120 mg of morphine sulfate, USP and the following inactive ingredients: ammoniomethacrylate copolymers, NF, fumaric acid, NF, povidone, USP, sodium lauryl sulfate, NF, sugar starch spheres, NF, and talc, USP.

The capsule shell contains black ink, gelatin, titanium dioxide, D&C yellow No. 10 (30 mg), FD&C blue No. 2 (45 mg), FD&C green No. 3 (60 mg), FDA iron oxide and FDA yellow iron oxide (75 mg), FD&C red No. 40 (90 mg), FD&C red No. 3 (120 mg), and FD&C blue No. 1 (120 mg).

The chemical name of morphine sulfate is 7,8-didehydro-4,5 alpha-epoxy-17-methylmorphinan-3,6 alpha-diol sulfate (2:1) (salt) pentahydrate with a molecular weight of 758. The empirical formula is $(C_{17}H_{19}NO_3)_2 \bullet H_2SO_4 \bullet 5H_2O$.

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



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Morphine sulfate, an opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine include drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system.

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

12.2 Pharmacodynamics

Plasma Level-Analgesia Relationships
While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. The effective dose in opioid-tolerant patients may be 10-50 times as great (or greater) than the appropriate dose for opioid-naïve individuals. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

CNS Depressant/Alcohol Interaction
Additive pharmacodynamic effects may be expected when AVINZA is used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Effects on the Central Nervous System
The principal therapeutic action of morphine is analgesia. Other therapeutic effects of morphine include anxiolysis, euphoria, and feelings of relaxation. Although the precise mechanism of the analgesic action is unknown, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. In common with other opioids, morphine causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. Morphine and related opioids depress the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose; however, when asphyxia is present during opioid overdose, marked mydriasis occurs.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
Gastric, biliary, and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result may be constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi. Morphine may also cause spasm of the sphincter of the urinary bladder.

Effects on the Cardiovascular System
In therapeutic doses, morphine does not usually exert major effects on the cardiovascular system. Morphine produces peripheral vasodilation which may result in orthostatic hypotension and fainting. Release of histamine can occur, which may play a role in opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

Effects on the Endocrine System
Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to hormonal changes that may manifest as symptoms of hypogonadism.

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

12.3 Pharmacokinetics

Absorption
AVINZA consists of two components, an immediate-release component and an extended-release component.

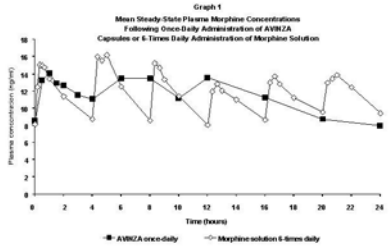
The oral bioavailability of morphine is less than 40% and shows large inter-individual variability due to extensive pre-systemic metabolism.

Following single-dose oral administration of a 60 mg dose of AVINZA under fasting conditions, morphine concentrations of approximately 3 to 6 ng/ml were achieved within 30 minutes after dosing and maintained for the 24-hour dosing interval. The pharmacokinetics of AVINZA were shown to be dose-proportional over a single oral dose range of 30 to 120 mg in healthy volunteers and a multiple oral dose range of at least 30 to 180 mg in patients with chronic moderate to severe pain.

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

Steady State: Steady-state plasma concentrations of morphine are achieved 2 to 3 days after initiation of once-daily administration of AVINZA.

AVINZA 60 mg Capsules (once-daily) and 10 mg morphine oral solution (6 times daily) were equally bioavailable.



A once-daily dose of AVINZA provided similar C_{max}, C_{min}, and AUC values and peak-trough fluctuations (% FL, C_{max}-C_{min}/C_{av}) compared to 6-times daily administration of the same total daily dose of morphine oral solution (Table 1).

Table 1 Pharmacokinetic Data Mean ± SD

Parameter	AVINZA Capsules Once-Daily	Morphine Oral Solution 6-Times Daily
AUC (ng/ml.h)	273.25 ± 81.24	279.11 ± 63.00
C_{max} (ng/ml)	18.65 ± 7.13	19.96 ± 4.82
C_{min} (ng/ml)	6.98 ± 2.44	6.61 ±2.15
% FL	106.38 ± 78.14	116.22 ±26.67

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

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

Excretion
Approximately 10% of a morphine dose is excreted unchanged in the urine. Elimination of morphine is primarily via hepatic metabolism to glucuronide metabolites M3G and M6G which are then renally excreted. A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic recycling. Seven to 10% of administered morphine is excreted in the feces. The mean adult plasma clearance of morphine is about 20 – 30 mL/minute/kg. The effective terminal half life of morphine after IV administration is reported to be approximately 2 hours. The terminal elimination half-life of morphine following single dose of AVINZA administration is approximately 24 hrs.

Specific Populations
Geriatric Patients
The pharmacokinetics of AVINZA have not been studied in elderly patients.

Pediatric Patients
The pharmacokinetics of AVINZA have not been studied in pediatric patients below the age of 18. The range of dose strengths available may not be appropriate for treatment of very young pediatric patients. Sprinkling on applesauce is **NOT** a suitable alternative for these patients.

Gender
A gender analysis of pharmacokinetic data from healthy subjects taking AVINZA indicated that morphine concentrations were similar in males and females.

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Studies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted.

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

Impairment of Fertility: No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites were seen. Studies from the literature have also reported changes in hormonal levels (i.e., testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.

14 CLINICAL STUDIES

AVINZA was studied in a double-blind, placebo-controlled, fixed-dose, parallel group trial in 295 patients with moderate to severe pain due to osteoarthritis. These patients had either a prior sub-optimal response to acetaminophen, NSAID therapy, or previously received intermittent opioid analgesic therapy. Thirty-milligrams AVINZA capsules administered once-daily, either in the morning or the evening, were more effective than placebo in reducing pain.

Table 2 Change from Baseline in WOMAC OA Index Pain VAS Subscale Score

Overall	Placebo	AVINZA QAM	AVINZA QPM
LS Mean	-36.23	-75.26[a]	-75.39[a]
Std. Error	11.482	11.305	11.747

a) P<0.05; REPEATED MEASURES ANALYSIS

This study was not designed to assess the effects of AVINZA on the course of the osteoarthritis.

16 HOW SUPPLIED/STORAGE AND HANDLING

30 mg extended-release capsule: size 3 capsule, yellow cap and white, opaque body imprinted AVINZA 30 mg and 505.
NDC 60793-605-01: Bottles of 100 capsules.
45 mg extended-release capsule: size 3 capsule, light blue cap and white, opaque body imprinted AVINZA 45 mg and 509.
NDC 60793-603-01: Bottles of 100 capsules.
60 mg extended-release capsule: size 3 capsule, bluish-green cap and white, opaque body imprinted AVINZA 60 mg and 506.
NDC 60793-606-01: Bottles of 100 capsules.
75 mg extended-release capsule: size 1 capsule, orange cap and white, opaque body imprinted AVINZA 75 mg and 510.
NDC 60793-604-01: Bottles of 100 capsules.
90 mg extended-release capsule: size 1 capsule, red cap and white, opaque body imprinted AVINZA 90 mg and 507.
NDC 60793-607-01: Bottles of 100 capsules.
120 mg extended-release capsule: size 1 capsule, blue-violet cap and white, opaque body imprinted AVINZA 120 mg and 508.
NDC 60793-608-01: Bottles of 100 capsules.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]
Protect from light and moisture.
Dispense in a tight, light-resistant container as defined in USP.
CAUTION: DEA Order Form Required.

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

Inform patients that potentially serious additive effects may occur if AVINZA is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a healthcare provider.

Important Administration Instructions
Instruct patients how to properly take AVINZA, including the following:

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

Hypotension
Inform patients that AVINZA may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Driving or Operating Heavy Machinery
Inform patients that AVINZA may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

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

Anaphylaxis
Inform patients that anaphylaxis has been reported with ingredients contained in AVINZA. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy
Advise female patients that AVINZA can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Disposal of Unused AVINZA
Advise patients to flush the unused capsules down the toilet when AVINZA is no longer needed.

Manufactured by:
Alkermes Gainesville LLC
Gainesville, GA 30504
Utilizing SODAS® Technology Developed by:

Alkermes Pharma Ireland Limited
Dublin, Ireland
U.S. Patent 6,066,339

SODAS® is a registered trademark of Alkermes Pharma Ireland Limited.

This product's label may have been updated. For current full prescribing information please visit www.pfizer.com.

LAB-0600-3.0

Medication Guide

AVINZA® (ah-ven-zah) (morphine sulfate) extended-release capsules, CII

AVINZA is:

- 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 AVINZA:

- **Get emergency help right away if you take too much AVINZA (overdose).** When you first start taking AVINZA, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Never give anyone your AVINZA. They could die from taking it. Store AVINZA away from children and in a safe place to prevent stealing or abuse. Selling or giving away AVINZA is against the law.

Do not take AVINZA if you have:

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

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

When taking AVINZA:

- Do not change your dose. Take AVINZA exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 24 hours, at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time the next day.
- Swallow AVINZA whole. Do not cut, break, chew, crush, dissolve, snort, or inject AVINZA because this may cause you to overdose and die.
- If you cannot swallow AVINZA 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 AVINZA without talking to your healthcare provider.**
- After you stop taking AVINZA, flush any unused capsules down the toilet.

While taking AVINZA DO NOT:

- Drive or operate heavy machinery, until you know how AVINZA affects you. AVINZA can make you sleepy, dizzy, or lightheaded.
- Drink alcohol, or use prescription or over-the-counter medicines containing alcohol. Using products containing alcohol during treatment with AVINZA may cause you to overdose and die.

The possible side effects of AVINZA are:

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

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.

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

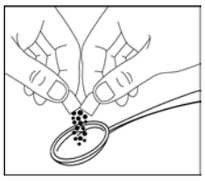
Manufactured for: Pfizer Inc, New York, NY 10017 by: Alkermes Gainesville LLC, Gainesville, GA, www.avinza.com or call 1-800-438-1985

This Medication Guide has been approved by the U.S. Food and Drug Administration
Revised: April 2014; LAB-0630-2.0

Instructions For Use
AVINZA ® (ah-ven-zah)
(morphine sulfate) extended-release Capsules, CII

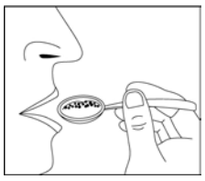
- If you cannot swallow AVINZA ® capsules, tell your healthcare provider. There may be another way to take AVINZA ® that may be right for you. If your healthcare provider tells you that you can take AVINZA® using this other way, follow these steps:

AVINZA® can be opened and the pellets inside the capsule can be sprinkled over applesauce, as follows:



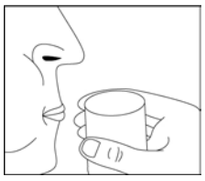
- Open the AVINZA® capsule and sprinkle the pellets over approximately one tablespoon of applesauce (See Figure 1).

Figure 1



- 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 2



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

Figure 3

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

Figure 4

You should not receive AVINZA® through a nasogastric tube or gastric tube (stomach tube).

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Manufactured for: Pfizer Inc, New York, NY 10017
by: Alkermes Gainesville LLC, Gainesville, GA

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