Pfizer Logo

FDA Approves Abuse Deterrent Labeling for EMBEDA® (morphine sulfate and naltrexone hydrochloride) Extended-Release (ER) Capsules CII

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EMBEDA is the first and only approved ER morphine specifically designed to deter oral and intranasal abuse when crushed

Pfizer Inc. (NYSE:PFE) announced today that the United States Food and Drug Administration (FDA) has approved an updated label for EMBEDA® (morphine sulfate and naltrexone hydrochloride) extended-release (ER) capsules, for oral use, CII, to include abuse-deterrence studies. The updated label states that EMBEDA has properties that are expected to reduce abuse via the oral and intranasal (i.e., snorting) routes when crushed. However, abuse of EMBEDA by these routes is still possible. The updated label also includes data from a human abuse potential study of intravenous (IV) morphine and naltrexone to simulate crushed EMBEDA. However, it is unknown whether the results with simulated crushed EMBEDA predict a reduction in abuse by the IV route until additional postmarketing data are available. EMBEDA 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. Pfizer expects EMBEDA will be available in the U.S. in early 2015.

“Prescription opioids are an important treatment option for people with chronic pain. However, misuse and abuse of opioids in the U.S. is a serious societal concern, which is why the development of abuse-deterrent formulations of these medicines is a high priority,” said Bob Twillman, Ph.D., Director of Policy and Advocacy, American Academy of Pain Management. “All opioid medications, including morphine products, have the potential for abuse. We believe that anything that can be done to reduce this risk is a significant development for healthcare providers and their patients.”

EMBEDA capsules consist of extended-release morphine sulfate and sequestered naltrexone hydrochloride, an opioid antagonist. Naltrexone is intended to remain sequestered when the product is taken as directed. The in vitro and pharmacokinetic data demonstrate that crushing EMBEDA pellets results in the simultaneous release and rapid absorption of morphine sulfate and naltrexone hydrochloride.

According to the Centers for Disease Control and Prevention, from 1999 to 2010, the number of fatal overdoses involving prescription opioids quadrupled, with more than 16,000 deaths in 2010 alone.[1] In 2012 the National Survey on Drug Use and Health reported that more than 12 million individuals in the U.S. used prescription opioids for non-medical purposes in the previous year. Approximately 70 percent of these non-medical prescription opioid users obtained them from a friend or relative.[2] Abuse-deterrent formulations (ADF) of opioid medications incorporate technology designed to make the product difficult to abuse, yet when used appropriately, they provide patients with pain relief comparable to non-abuse deterrent formulation opioids.

“More than one-third of extended-release opioids prescribed are morphine, and EMBEDA is the first extended-release morphine with the potential to reduce abuse via the oral and intranasal routes when crushed,” said Dr. Steven Romano, senior vice president and head, Medicines Development Group, Pfizer Global Innovative Pharmaceutical Business. “Pfizer believes that abuse-deterrent products, like EMBEDA, are important to help address the growing public health problem of opioid abuse in the U.S.”

Pfizer supports the appropriate use of opioid pain medications and has other products in development incorporating abuse deterrent technology. EMBEDA is the first and only approved morphine specifically designed to deter certain forms of abuse. Pfizer has decided to remove its non-abuse deterrent morphine formulation, AVINZA® (morphine sulfate) extended-release capsules CII from the U.S. market and notified the FDA earlier this year of the intent to discontinue manufacturing of the product. 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.

About EMBEDA

EMBEDA® (morphine sulfate and naltrexone hydrochloride) extended-release capsules CII 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 EMBEDA 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.

EMBEDA is not indicated as an as-needed (prn) analgesic.

EMBEDA Important Safety Information

BOXED WARNING:

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

Addiction, Abuse, and Misuse

EMBEDA® (morphine sulfate and naltrexone hydrochloride) extended-release capsules, for oral use, CII 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 EMBEDA, and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of EMBEDA. Monitor for respiratory depression, especially during initiation of EMBEDA or following a dose increase. Instruct patients to swallow EMBEDA capsules whole or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing or dissolving EMBEDA can cause rapid release and absorption of a potentially fatal dose of morphine.

Accidental Ingestion

Accidental ingestion of even one dose of EMBEDA, especially by children, can result in a fatal overdose of morphine.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of EMBEDA 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.

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking EMBEDA. The co-ingestion of alcohol with EMBEDA may result in increased plasma levels and a potentially fatal overdose of morphine.

Contraindications

EMBEDA 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, or hypersensitivity (e.g., anaphylaxis) to morphine or naltrexone.

Addiction, Abuse, and Misuse

EMBEDA contains morphine a Schedule II controlled substance. As an opioid, EMBEDA exposes users to the risks of addiction, abuse, and misuse. As modified-release products such as EMBEDA 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 EMBEDA 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 EMBEDA, and monitor all patients receiving EMBEDA 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). Patients at increased risk may be prescribed modified-release opioid formulations such as EMBEDA, but use in such patients necessitates intensive counseling about the risks and proper use of EMBEDA along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of EMBEDA 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. Misuse or abuse of EMBEDA by these methods may also release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals.

Opioid agonists such as EMBEDA are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing EMBEDA. 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.

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. Carbon dioxide (CO2) 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 EMBEDA, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with EMBEDA and following dose increases.

Accidental Ingestion

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of EMBEDA 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.

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.

Interaction with Central Nervous System Depressants

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on EMBEDA therapy. The co-ingestion of alcohol with EMBEDA may result in increased plasma levels and a potentially fatal overdose of morphine. Hypotension profound sedation, coma, respiratory depression, and death may result if EMBEDA is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotic, neuroleptics, other opioids).

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 EMBEDA and when EMBEDA is given concomitantly with other drugs that depress respiration.

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, as in these patients, even usual therapeutic doses of EMBEDA may decrease respiratory drive to the point of apnea. Consider the use of alternative non-opioid analgesics in these patients if possible.

Hypotensive Effect

EMBEDA 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. Monitor these patients for signs of hypotension after initiating or titrating the dose of EMBEDA. In patients with circulatory shock, EMBEDA may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of EMBEDA in patients with circulatory shock.

Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking EMBEDA who may be susceptible to the intracranial effects of CO2 retention for signs of sedation and respiratory depression as EMBEDA may reduce respiratory drive and the resultant CO2 retention can further increase intracranial pressure. Avoid the use of EMBEDA in patients with impaired consciousness or coma.

Use in Patients with Gastrointestinal Conditions

EMBEDA is contraindicated in patients with paralytic ileus. Avoid the use of EMBEDA in patients with other GI obstruction. The morphine in EMBEDA 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.

Use in Patients with Convulsive or Seizure Disorders

The morphine in EMBEDA may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings.

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 full opioid agonist analgesic including EMBEDA. In these patients mixed agonists/antagonists and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

Consuming EMBEDA capsules that have been altered by crushing, chewing or dissolving the pellets can release sufficient naltrexone to precipitate withdrawal in opioid–dependent individuals. Symptoms of withdrawal usually appear within 5 minutes and can last up to 48 hours. When discontinuing EMBEDA, gradually taper the dose and do not abruptly discontinue.

Driving and Operating Machinery

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

Adverse Reactions

Most common adverse reactions (>10%) are constipation, nausea, and somnolence.

Administration Considerations

Individualize dosing based on patient's prior analgesic treatment experience and risk factors for addiction, abuse and misuse, and titrate as needed to provide adequate analgesia and minimize adverse reactions. When EMBEDA is the first opioid analgesic, initiate EMBEDA therapy with the 20 mg/0.8 mg capsule orally every 24 hours. Instruct patients to swallow EMBEDA capsules intact or to sprinkle the capsule contents on applesauce and immediately swallow without chewing. The capsules contain pellets that consist of morphine and sequestered naltrexone. Crushing, chewing or dissolving the pellets in EMBEDA will result in rapid release and absorption of a potentially fatal dose of morphine. Consuming EMBEDA capsules that have been altered by crushing, chewing, or dissolving the pellets can release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals.

EMBEDA 100 mg/4 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.

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

Drug Interactions

- Concomitant use of alcohol with EMBEDA can result in an increase of morphine plasma levels and potentially fatal overdose of morphine.
- Concomitant use of EMBEDA and other CNS depressants (e.g. sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids and alcohol) can increase the risk of respiratory depression, profound sedation, coma and death.
- Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of EMBEDA and/or may precipitate withdrawal symptoms. Avoid the use of agonist/antagonist and partial agonist analgesics in patients receiving EMBEDA.
- Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
- The effects of morphine may be potentiated by monoamine oxidase inhibitors (MAOIs). MAOIs have been reported to potentiate the effects of morphine anxiety, confusion, and significant depression of respiration or coma. EMBEDA should not be used in patients taking MAOIs or within 14 days of stopping such treatment.
- 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.
- 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.
- Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
- P-Glycoprotein (PGP) inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine by about two-fold.

Please see Full Prescribing Information including BOXED WARNING and Medication Guide.

About AVINZA

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.

AVINZA Important Safety Information

BOXED WARNING:

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

Addiction, Abuse, and Misuse

AVINZA® (morphine sulfate) extended-release capsules, for oral use, CII 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.

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.

Accidental Ingestion

Accidental ingestion of even one dose of AVINZA, especially by children, can result in a fatal overdose of morphine.

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.

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.

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; or hypersensitivity (e.g., anaphylaxis) to morphine.

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. 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). 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.

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.

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. 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.

Accidental Ingestion

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

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.

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.

Interaction 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. 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).

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.

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, as in these patients, even usual therapeutic doses of AVINZA may decrease respiratory drive to the point of apnea. Consider the use of alternative non-opioid analgesics in these patients if possible.

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. 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.

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 for signs of sedation and respiratory depression as AVINZA may reduce respiratory drive and the resultant CO_2 retention can further increase intracranial pressure. Avoid the use of AVINZA in patients with impaired consciousness or coma.

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.

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.

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 an 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 and do not abruptly discontinue.

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.

Adverse Reactions

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

Administration Considerations

Individualize dosing based on patient’s prior analgesic treatment experience and risk factors for addiction, abuse, and misuse, and titrate as needed to provide adequate analgesia and minimize adverse reactions. When AVINZA is the first opioid analgesic, initiate AVINZA therapy with 30 mg capsule orally every 24-hour and adjust the dose of AVINZA in increments not greater than 30 mg every 3 to 4 days. Instruct patients to swallow AVINZA capsules intact, or to sprinkle the capsule contents on applesauce and immediately swallow without chewing. Crushing, chewing, or dissolving the pellets in AVINZA will result in uncontrolled delivery of morphine and can lead to overdose or death.

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.

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

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.

Drug Interactions

- Concomitant use of alcohol with AVINZA can result in an increase of morphine plasma levels and potentially fatal overdose of morphine.
- Concomitant use of AVINZA and other CNS depressants (eg, sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids and alcohol) can increase the risk of respiratory depression, profound sedation, coma, and death.
- 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.
- Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
- The effects of morphine may be potentiated by monoamine oxidase inhibitors (MAOIs). 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.
- 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.
- 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.
- Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
- P-Glycoprotein (PGP) inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine by about two-fold.

Please see Full Prescribing Information including BOXED WARNING and Medication Guide.

Pfizer Inc.: Working together for a healthier world®

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, Pfizer has worked to make a difference for all who rely on us. To learn more, please visit us at www.pfizer.com.

DISCLOSURE NOTICE: The information contained in this release is as of October 17, 2014. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about EMBEDA® (morphine sulfate and naltrexone hydrochloride) extended-release capsules CII and certain investigational products, which involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Forward-looking statements include those about EMBEDA's potential benefits and the anticipated timing of its availability in the U.S., and statements about other investigational products in development incorporating abuse deterrent technology. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical study commencement and completion dates as well as the possibility of unfavorable study results; risks associated with Pfizer's ability to meet anticipated product availability dates; uncertainty regarding the commercial success of EMBEDA; whether and when any applications may be submitted with regulatory authorities for investigational products in development incorporating abuse deterrent technology; whether and when any such regulatory authorities may approve any such applications, as well as their decisions regarding labeling and other matters that could affect the availability or commercial potential of any such investigational products; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2013 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the SEC and available at www.sec.gov and www.pfizer.com.

[1] Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report* 2013;62(12):234.

[2] *Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings*, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: SAMHSA; 2013.

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