EMBEDA® (II)
(morphine sulfate and naltrexone HCl)
Extended-Release Capsules for oral use, 20 mg/0.8 mg

EMBEDA Pharmacy Services

INDICATION
EMBEDA® (morphine sulfate and naltrexone HCl) Extended-Release Capsules, for oral use, 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.

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.

Please see Full Prescribing Information, including BOXED WARNING and Medication Guide, in pocket. Please see additional Important Safety Information continued throughout.

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USE THE PFIZER OPIOID PRESCRIPTION PORTAL TO HELP YOUR PATIENTS OBTAIN EMBEDA

Visit **PfizerOpioidRx.com** to create a portal login and fill your patient's prescription using the Pharmacy Locator or Home Delivery Services

Pharmacy Locator

With this service, you may e-prescribe to a local pharmacy that has EMBEDA® (morphine sulfate and naltrexone HCl) Extended-Release Capsules, for oral use, CII in stock or will have it in stock within 24 to 48 hours. This service will preclear your patient's insurance before selecting the pharmacy.

Please note that all states support e-prescribing of CII products, but it does require additional certification. For more information, work with your EHR system.

Using your portal login, you may confirm that your patient was able to pick up their prescription.

Home Delivery

With this service, you may enroll your patients to have their prescription delivered to their home. After enrollment, the service will obtain pre-approval of your patient's insurance (including prior authorization if required). You may provide a physical prescription or e-prescription to the assigned specialty pharmacy.

Physical prescription:
A prepaid, overnight FedEx label will be provided to your patient with the pharmacy's address prepopulated. Using this label, your patient can mail their prescription and will receive their medication from the specialty pharmacy within 2 to 3 days.

Please note that a formal FedEx envelope is not required; a manila envelope would be sufficient.

E-prescription:
This process expedites delivery to 1 to 2 days.

Please note that all states support e-prescribing of CII products, but it does require additional certification. For more information, work with your EHR system.

The medication will be delivered to your patient in a confidential package and will require the signature of someone 18 years of age or older.

A home delivery representative will notify you and your patient 10 days before the prescription needs to be refilled.

This 10-day notification is important because of the DEA requirement prohibiting new CII prescriptions from being written until day 30. If your patient waits until their prescription runs out, they may be without their medication for 1 to 2 days.

Your patient may also call these services directly

When you prescribe EMBEDA, provide your patients with the tear-off sheet containing the contact information for the Pharmacy Locator and Home Delivery Services.

Your patient may call **1-800-682-7796** to speak to a pharmacy locator representative who will preclear your patient's insurance and locate 1 to 3 pharmacies that can fill their EMBEDA prescription.

The pharmacy locator representative will also ask your patient if they would like to enroll in the Home Delivery Service.

Your patient may call **1-844-214-3441** to speak to a home delivery representative who will enroll them in the Home Delivery Service.

If your patient is eligible for a copay card but was not offered one, the home delivery representative will direct them to EMBEDA.com to register for one.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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 (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 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.

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.

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, hypnotics, neuroleptics, other opioids).

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The Pharmacy Locator and Home Delivery Services:

- Give you confidence that your patients will be able to fill their EMBEDA® (morphine sulfate and naltrexone HCl) Extended-Release Capsules, for oral use, CII prescription
- Reduce patient call-backs to your office
- Provide a more convenient way for patients to receive their EMBEDA prescription
- Ensure that patient information and communications are kept confidential
- Remind you and your patients when to expect refills

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IMPORTANT SAFETY INFORMATION (CONTINUED)

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 CO_2 retention for signs of sedation and respiratory depression as EMBEDA may reduce respiratory drive and the resultant CO_2 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.

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