



King Pharmaceuticals, Inc.
Research and Development
CentreGreen Two, Suite 300
4000 CentreGreen Way
Cary, NC 27513

Eric G. Carter, PhD, MD
Chief Science Officer

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Dear Pharmacist:

King Pharmaceuticals[®], Inc. would like to notify you that EMBEDA[™] (morphine sulfate and naltrexone hydrochloride) Extended Release Capsule CII has been approved for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. EMBEDA[™] Capsules contain pellets of morphine sulfate, an opioid receptor agonist with a sequestered core of naltrexone hydrochloride. EMBEDA[™] is intended for oral use only.

The purpose of this communication is to notify you of the Food and Drug Administration (FDA) requirement to distribute a copy of the enclosed Medication Guide to the patient with each prescription filled for EMBEDA[™].

In order to ensure that the benefits of EMBEDA[™] outweigh the potential risks of EMBEDA[™], a Risk Evaluation and Mitigation Strategy (REMS) has been implemented in response to a requirement of the FDA. The goals of this REMS are:

- To inform patients and providers about the potential for abuse, misuse, overdose and addiction of EMBEDA[™]
- To inform patients and providers about the safe use of EMBEDA[™]

Please see the attached Full Prescribing Information, including the boxed warning, and Medication Guide for important safety information for EMBEDA[™].

It is important that you discuss the risks of EMBEDA[™] with your patients and their caregivers and encourage them to read the Medication Guide. The Medication Guide provides important information on the safe and effective use of EMBEDA[™] Capsules. Patients should be counseled on the need to store EMBEDA[™] safely out of the reach of children and household acquaintances.

Potential for abuse, misuse, overdose and addiction of EMBEDA[™]:

EMBEDA[™] Capsules contain morphine, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid agonists. EMBEDA[™] can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing EMBEDA[™] in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

EMBEDA[™] 100 mg/4 mg Capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.

Patients should not consume alcoholic beverages while on EMBEDA[™] therapy. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on EMBEDA[™] therapy. The co-ingestion of alcohol with EMBEDA[™] may result in an increase of plasma levels and potentially fatal overdose of morphine.

EMBEDA[™] Capsules are to be swallowed whole or the contents of the capsules sprinkled on apple sauce. EMBEDA[™] contains pellets of extended release morphine formulated around a sequestered core of naltrexone, an opioid antagonist. The pellets in the capsules are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of morphine. Crushing, chewing, or dissolving EMBEDA[™] will also result in the release of naltrexone which may precipitate withdrawal in opioid-tolerant individuals.

Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. 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.

Abuse of EMBEDA™ by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death. Tampering with EMBEDA™ in this way will also release naltrexone and in opioid tolerant individuals this increases the risk of precipitating withdrawal.

EMBEDA™ may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Safe Use of EMBEDA™:

EMBEDA™ is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

EMBEDA™ is NOT intended for use as a prn analgesic. EMBEDA™ is not indicated for acute/postoperative pain or if the pain is mild or not expected to persist for an extended period of time. EMBEDA™ Capsules are only indicated for postoperative use if the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate.

EMBEDA™ is contraindicated in patients with a known hypersensitivity to morphine, morphine salts, naltrexone, or in any situation where opioids are contraindicated, and in patients with significant respiratory depression, acute or severe bronchial asthma, and hypercapnia (in unmonitored settings or the absence of resuscitative equipment). EMBEDA™ is contraindicated in any patient who has or is suspected of having paralytic ileus.

Respiratory depression is the chief hazard of all morphine preparations such as EMBEDA™. Respiratory depression occurs more frequently and is more dangerous in elderly and debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction (when even moderate therapeutic doses may significantly decrease pulmonary ventilation).

EMBEDA™ should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. EMBEDA™ can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in pressure in patients with head injuries. EMBEDA™ should only be administered under such circumstances when considered essential and then with extreme care.

EMBEDA™ should be administered with caution, and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; patients with Addison disease; myxedema; hypothyroidism; prostatic hypertrophy or urethral stricture. Caution should also be exercised in the administration of EMBEDA™ to patients with CNS depression, toxic psychosis, acute alcoholism, and delirium tremens. All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Care should be taken to use low initial doses of EMBEDA™ in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications.

Consuming EMBEDA™ that has been tampered with by crushing, dissolving, or chewing the extended-release formulation can release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals. Symptoms of withdrawal usually appear within 5 minutes of ingestion of naltrexone and can last for up to 48 hours. Mental status changes can include confusion, somnolence, and visual hallucinations. Significant fluid losses from vomiting and diarrhea can require intravenous fluid administration. Patients should be closely monitored and therapy with non-opioid medications should be tailored to meet individual requirements.

Serious adverse events associated with EMBEDA™ in clinical use include respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock. Common adverse events reported during initiation of EMBEDA™ therapy include drowsiness, dizziness, constipation, and nausea. The most common adverse events reported during clinical studies include constipation, nausea and somnolence.

In general, EMBEDA™ should not be abruptly discontinued. However, EMBEDA™, like other opioids, can be safely discontinued without the development of withdrawal symptoms by slowly tapering the daily dose.

Two Medication Guides will be provided in each EMBEDA™ Capsule 100 count bottle. If you require additional Medication Guides you may:


- Contact King Professional Information Services Department at 800-776-3637
- Print copies from the EMBEDA™ website (www.embeda.com)
- Request additional Medication Guides from your drug supplier

Please report all suspected adverse events associated with the use of EMBEDA™ to King Pharmaceuticals, Inc., Attention: Drug Safety and Pharmacovigilance at 4000 CentreGreen Way, Suite 300, Cary, NC 27513 or by phone at 1-800-546-4905.

Adverse event information may also be reported to the FDA MedWatch Reporting System by phone at 1-800-FDA-1088 or by mail using Form 3500 at www.fda.gov/medwatch.

Please take the time to review the enclosed Full Prescribing Information and Medication Guide. If you have any questions or concerns, you may contact our Professional Information Services Department at 800-776-3637 or visit www.embeda.com.

Sincerely,



Eric Carter, PhD, MD
Chief Science Officer