

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EMBEDA safely and effectively. See full prescribing information for EMBEDA.

EMBEDA® (morphine sulfate and naltrexone hydrochloride) extended-release capsules, for oral use, CII  
Initial U.S. Approval: 2009

**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.

- EMBEDA 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 EMBEDA capsules whole to avoid exposure to a potentially fatal dose of morphine. (5.2)
- Accidental ingestion of EMBEDA, especially in children, can result in fatal overdose of morphine. (5.2)
- Prolonged use of EMBEDA 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 EMBEDA 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

EMBEDA is a combination opioid agonist/opioid antagonist product 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 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.(1)
- EMBEDA is not indicated as an as-needed (prn) analgesic. (1)

### DOSAGE AND ADMINISTRATION

- 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. (2.1)

- For opioid-naïve and opioid non-tolerant patients, initiate with 20 mg/0.8 mg capsules (morphine sulfate/naltrexone hydrochloride) orally every 24 hours. (2.1)
- Do not abruptly discontinue EMBEDA in a physically-dependent patient. (2.3, 5.11)
- Instruct patients to swallow EMBEDA capsules intact, or to sprinkle the capsule contents on applesauce and immediately swallow without chewing. (2.4)
- Instruct patients not to crush, dissolve, or chew the pellets in the capsule to avoid the risk of release and absorption of a potentially fatal dose of morphine, and to avoid release of sequestered naltrexone that could precipitate opioid withdrawal. (2.4)

### DOSAGE FORMS AND STRENGTHS

Extended-release capsules (morphine sulfate/naltrexone hydrochloride): 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg (3)

### CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Hypersensitivity to morphine or naltrexone (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 EMBEDA in patients with impaired consciousness or coma susceptible to intracranial effects of CO<sub>2</sub> retention. (5.8)

### ADVERSE REACTIONS

Most common adverse reactions (>10%): constipation, nausea, and somnolence. (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](http://www.fda.gov/medwatch)

### DRUG INTERACTIONS

- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with EMBEDA because they may reduce analgesic effect of EMBEDA or precipitate withdrawal symptoms. (5.11, 7.3)
- Monoamine oxidase inhibitors (MAOIs): Avoid EMBEDA 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 EMBEDA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2014

---

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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

**Boxed Warning**

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Initial Dosing
- 2.2 Titration and Maintenance of Therapy
- 2.3 Discontinuation of EMBEDA
- 2.4 Administration of EMBEDA

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Addiction, Abuse, and Misuse
- 5.2 Life-Threatening Respiratory Depression
- 5.3 Neonatal Opioid Withdrawal Syndrome
- 5.4 Interactions with Central Nervous System Depressants
- 5.5 Use in Elderly, Cachectic, and Debilitated Patients
- 5.6 Use in Patients with Chronic Pulmonary Disease
- 5.7 Hypotensive Effect
- 5.8 Use in Patients with Head Injury or Increased Intracranial Pressure
- 5.9 Use in Patients with Gastrointestinal Conditions
- 5.10 Use in Patients with Convulsive or Seizure Disorders
- 5.11 Avoidance of Withdrawal
- 5.12 Driving and Operating Machinery
- 5.13 Interference with Laboratory Tests

**6 ADVERSE REACTIONS**

- 6.1 Clinical Studies Experience

**7 DRUG INTERACTIONS**

- 7.1 Alcohol

- 7.2 CNS Depressants

- 7.3 Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

- 7.4 Muscle Relaxants

- 7.5 Monoamine Oxidase Inhibitors (MAOIs)

- 7.6 Cimetidine

- 7.7 Diuretics

- 7.8 Anticholinergics

- 7.9 P-Glycoprotein (P-gp) Inhibitors

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy

- 8.2 Labor and Delivery

- 8.3 Nursing Mothers

- 8.4 Pediatric Use

- 8.5 Geriatric Use

**9 DRUG ABUSE AND DEPENDENCE**

- 9.1 Controlled Substance

- 9.2 Abuse

- 9.3 Dependence

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action

- 12.2 Pharmacodynamics

- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

\* 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**

EMBEDA<sup>®</sup> 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 [*see Warnings and Precautions (5.1)*].

#### **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 [*see Warnings and Precautions (5.2)*].

#### **Accidental Ingestion**

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

#### **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 [*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 EMBEDA. The co-ingestion of alcohol with EMBEDA may result in increased plasma level and a potentially fatal overdose of morphine [*see Warnings and Precautions (5.4)*].

## **1 INDICATIONS AND USAGE**

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.

### **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.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Initial Dosing**

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

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.

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 EMBEDA [*see Warnings and Precautions (5.2)*].

EMBEDA capsules must be taken whole. Crushing, chewing, or dissolving EMBEDA 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 EMBEDA

should be instructed to sprinkle the capsule contents on applesauce and immediately swallow without chewing [see *Administration of EMBEDA* (2.4)].

EMBEDA is administered at a frequency of either once daily (every 24 hours) or twice daily (every 12 hours).

#### *Use of EMBEDA as the First Opioid Analgesic*

Initiate treatment with EMBEDA with 20 mg/0.8 mg capsule orally every 24 hours.

#### *Use of EMBEDA in Patients who are not Opioid Tolerant*

The starting dose for patients who are not opioid tolerant is EMBEDA 20 mg/0.8 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 EMBEDA*

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

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

#### *Conversion from Other Oral Morphine Formulations to EMBEDA*

Patients receiving other oral morphine formulations may be converted to EMBEDA by administering one-half of the patient's total daily oral morphine dose as EMBEDA twice daily, or by administering the total daily oral morphine dose as EMBEDA once daily. There are no data to support the efficacy or safety of prescribing EMBEDA more frequently than every 12 hours.

#### *Conversion from Parenteral Morphine, or Other Opioids, to EMBEDA*

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

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

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

#### *Conversion from Methadone to EMBEDA*

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

## **2.2 Titration and Maintenance of Therapy**

Individually titrate EMBEDA to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving EMBEDA 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 EMBEDA dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within 24 to 36 hours, EMBEDA dose may be adjusted every 1 to 2 days.

Patients who experience breakthrough pain may require a dose increase of EMBEDA, 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 EMBEDA dose. In patients experiencing inadequate analgesia with once-daily dosing of EMBEDA, consider a twice-daily regimen.

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 EMBEDA

When a patient no longer requires therapy with EMBEDA, 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 EMBEDA.

### 2.4 Administration of EMBEDA

Instruct patients to swallow EMBEDA capsules intact. The capsules contain pellets that consist of morphine and sequestered naltrexone. 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 [see *Warnings and Precautions* (5.2)]. 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 [see *Warnings and Precautions* (5.12)].

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

Do not administer EMBEDA pellets through a nasogastric or gastric tube.

## 3 DOSAGE FORMS AND STRENGTHS

EMBEDA capsules contain creamy white to light tan spheroidal pellets, have an outer opaque capsule with colors as identified below and are available in six dosage strengths.

Each 20 mg/0.8 mg extended-release capsule contains 20 mg of morphine sulfate and 0.8 mg of naltrexone hydrochloride in a two-toned yellow opaque capsule with “EMBEDA” printed in grey ink on the darker-toned cap and a single grey band around  $\frac{3}{4}$  of the circumference. The lighter-toned body has “20” reverse-printed in a grey circle.

Each 30 mg/1.2 mg extended-release capsule contains 30 mg of morphine sulfate and 1.2 mg of naltrexone hydrochloride in a two-toned blue-violet opaque capsule with “EMBEDA” printed in grey ink on the darker-toned cap and a single grey band around  $\frac{3}{4}$  of the circumference. The lighter-toned body has “30” reverse-printed in a grey circle.

Each 50 mg/2 mg extended-release capsule contains 50 mg of morphine sulfate and 2 mg of naltrexone hydrochloride in a two-toned blue opaque capsule with “EMBEDA” printed in grey ink on the darker-toned cap and a single grey band around  $\frac{3}{4}$  of the circumference. The lighter-toned body has “50” reverse-printed in a grey circle.

Each 60 mg/2.4 mg extended-release capsule contains 60 mg of morphine sulfate and 2.4 mg of naltrexone hydrochloride in a two-toned pink opaque capsule with “EMBEDA” printed in grey ink on the darker-toned cap and a single grey band around  $\frac{3}{4}$  of the circumference. The lighter-toned body has “60” reverse-printed in a grey circle.

Each 80 mg/3.2 mg extended-release capsule contains 80 mg of morphine sulfate and 3.2 mg of naltrexone hydrochloride in a two-toned light peach opaque elongated capsule with “EMBEDA” printed in grey ink on the darker-toned cap and a single grey band around  $\frac{3}{4}$  of the circumference. The lighter-toned body has “80” reverse-printed in a grey circle.

Each 100 mg/4 mg extended-release capsule contains 100 mg of morphine sulfate and 4 mg of naltrexone hydrochloride in a two-toned green opaque capsule with “EMBEDA” printed in grey ink on the darker-toned cap and a single grey band around  $\frac{3}{4}$  of the circumference. The lighter-toned body has “100” reverse-printed in a grey circle.

## 4 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
- Hypersensitivity (e.g., anaphylaxis) to morphine or naltrexone [*see Adverse Reactions (6.1)*]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 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 [*see Drug Abuse and Dependence (9)*]. 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). The potential for these risks should not, however, prevent the prescribing of EMBEDA for the proper management of pain in any given patient. 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 [*see Overdosage (10)*]. Misuse or abuse of EMBEDA by these methods may also release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals [*see Warnings and Precautions (5.11)*].

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 [*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<sub>2</sub>) 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.

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

Accidental ingestion of even one dose of EMBEDA, 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 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 drug elimination 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 EMBEDA therapy. The co-ingestion of alcohol with EMBEDA 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 EMBEDA 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 EMBEDA 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 EMBEDA is made, start with EMBEDA 20 mg/0.8 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 EMBEDA and when EMBEDA 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 EMBEDA, as in these patients, even usual therapeutic doses of EMBEDA 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**

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 (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 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.

#### **5.8 Use in Patients with Head Injury or Increased Intracranial Pressure**

Monitor patients taking EMBEDA who may be susceptible to the intracranial effects of CO<sub>2</sub> 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 EMBEDA. EMBEDA may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

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

#### **5.9 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 serum amylase.

#### **5.10 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. Monitor patients with a history of seizure disorders for worsened seizure control during EMBEDA 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 full opioid agonist analgesic, including EMBEDA. In these patients, mixed agonists/antagonist 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 five minutes of ingestion of naltrexone and can last for up to 48 hours. Mental status changes can include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Significant fluid losses from vomiting and diarrhea can require intravenous (IV) fluid administration.

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

### 5.12 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.

### 5.13 Interference with Laboratory Tests

Naltrexone does not interfere with thin-layer, gas-liquid, and high performance liquid chromatographic methods which may be used for the separation and detection of morphine, methadone, or quinine in the urine. Naltrexone may or may not interfere with enzymatic methods for the detection of opioids depending on the specificity of the test. Consult the test manufacturer for specific details.

## 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)*]

In the randomized study, the most common adverse reactions with EMBEDA therapy were constipation, nausea, and somnolence. The most common adverse reactions leading to study discontinuation were nausea, constipation (sometimes severe), vomiting, fatigue, dizziness, pruritus, 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.

#### *Short-Term Randomized Study*

This study utilized an enriched enrollment with a randomized withdrawal design in which subjects were titrated to effect on open-label EMBEDA for up to 45 days. Once their pain was controlled, 344 of 547 subjects were randomized to either an active treatment with EMBEDA or were tapered off EMBEDA using a double-dummy design and placed on placebo. The maintenance Period was 12 weeks. Adverse reactions, reported in  $\geq 2\%$  of subjects in either the titration or maintenance phase of the 12-week study are presented in Table 1.

**Table 1: Adverse Reactions Reported in  $\geq 2\%$  of Subjects in the Randomized Study**

Adverse Reaction	Titration	Maintenance	
	EMBEDA (N=547) n (%)	EMBEDA (N=171) n (%)	Placebo (N=173) n (%)
Constipation	165 (30%)	12 (7%)	7 (4%)
Nausea	106 (19%)	19 (11%)	11 (6%)
Somnolence	76 (14%)	2 (1%)	5 (3%)
Vomiting	46 (8%)	7 (4%)	2 (1%)
Dizziness	42 (8%)	2 (1%)	2 (1%)
Pruritus	34 (6%)	0	1 (1%)
Dry mouth	31 (6%)	3 (2%)	2 (1%)
Headache	22 (4%)	4 (2%)	2 (1%)
Fatigue	16 (3%)	1 (1%)	2 (1%)
Insomnia	7 (1%)	5 (3%)	4 (2%)
Diarrhea	6 (1%)	12 (7%)	12 (7%)
Abdominal pain upper	6 (1%)	4 (2%)	3 (2%)
Flushing	0	4 (2%)	1 (1%)

***Long-Term Open-Label Safety Study***

In the long-term open-label safety study, 465 patients with chronic non-malignant pain were enrolled and 124 patients were treated for up to 1 year. The distributions of adverse events were similar to that of the randomized, controlled studies, and were consistent with the most common opioid-related adverse reactions. Adverse reactions reported in  $\geq 2.0\%$  of subjects are presented in Table 2.

**Table 2: Adverse Reactions Reported by  $\geq 2.0\%$  of Subjects in Long-Term Safety Study**

Adverse Reaction	EMBEDA (N=465) n (%)
Constipation	145 (31%)
Nausea	103 (22%)
Vomiting	37 (8%)
Somnolence	34 (7%)
Headache	32 (7%)
Pruritus	26 (6%)
Fatigue	19 (4%)
Dizziness	19 (4%)
Dry mouth	17 (4%)
Hyperhidrosis	16 (3%)
Insomnia	13 (3%)
Diarrhea	10 (2%)
Anxiety	10 (2%)

***Adverse Reactions Observed in the Phase 2/3 Studies***

Most common ( $\geq 10\%$ ): constipation, nausea, somnolence

Common ( $\geq 1\%$  to  $<10\%$ ): vomiting, headache, dizziness, pruritus, dry mouth, diarrhea, fatigue, insomnia, hyperhidrosis, anxiety, chills, abdominal pain, lethargy, edema peripheral, dyspepsia, anorexia, muscle spasms, depression, flatulence, restlessness, decreased appetite, irritability, stomach discomfort, tremor, arthralgia, hot flush, sedation

Less Common ( $<1\%$ ):

*Eye disorders:* vision blurred, orthostatic hypotension

*Gastrointestinal disorders:* abdominal distension, pancreatitis, abdominal discomfort, fecaloma, abdominal pain lower, abdominal tenderness

*General disorders and administration site conditions:* malaise, asthenia, feeling jittery, drug withdrawal syndrome

*Hepatobiliary disorders:* cholecystitis

*Investigations:* alanine aminotransferase increased, aspartate aminotransferase increased

*Musculoskeletal and connective tissue disorders:* myalgia, muscular weakness

*Nervous system disorders:* depressed level of consciousness, mental impairment, memory impairment, disturbance in attention, stupor, paresthesia, coordination abnormal

*Psychiatric disorders:* disorientation, thinking abnormal, mental status changes, confusional state, euphoric mood, hallucination, abnormal dreams, mood swings, nervousness

*Renal and urinary disorders:* urinary retention, dysuria

*Reproductive system and breast disorders:* erectile dysfunction

*Respiratory, thoracic and mediastinal disorders:* dyspnea, rhinorrhea

*Skin and subcutaneous tissue disorders:* rash, piloerection, cold sweat, night sweats

*Vascular disorders:* hypotension, flushing

Anaphylaxis has been reported with ingredients contained in EMBEDA. 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 EMBEDA 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 EMBEDA therapy [*see Clinical Pharmacology (12.3)*].

### **7.2 CNS Depressants**

The concomitant use of EMBEDA 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 EMBEDA 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 EMBEDA and/or may precipitate withdrawal symptoms. Avoid the use of agonist/antagonist and partial agonist analgesics in patients receiving EMBEDA.

### **7.4 Muscle Relaxants**

Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and EMBEDA 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 EMBEDA 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. EMBEDA 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 EMBEDA 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 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. Monitor patients for signs of urinary retention or reduced gastric motility when EMBEDA is used concurrently with anticholinergic drugs.

## 7.9 P-Glycoprotein (P-gp) Inhibitors

P-gp inhibitors (e.g., quinidine) may increase the absorption/exposure of morphine by about two-fold. Monitor patients for signs of respiratory and CNS depression when P-gp inhibitors are used concurrently with EMBEDA.

# 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. EMBEDA 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 occurred 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 sternbrae, 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<sub>2</sub> and increased risk of sudden infant death syndrome. Morphine 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. EMBEDA 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 EMBEDA.

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 EMBEDA, 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 efficacy of EMBEDA in patients less than 18 years of age have not been established.

### **8.5 Geriatric Use**

Clinical studies of EMBEDA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. The pharmacokinetics of EMBEDA have not been investigated in elderly patients (>65 years) although such patients were included in clinical studies. In a long-term open-label safety study, the pre-dose plasma morphine concentrations after dose normalization were similar for subjects <65 years and those ≥65 years of age. Limited data are available on the pharmacokinetics of EMBEDA in geriatric patients [*see Clinical Pharmacology (12.3)*].

## **9 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

EMBEDA contains morphine, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. EMBEDA 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 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.

EMBEDA, 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 EMBEDA

EMBEDA is for oral use only. Abuse of EMBEDA poses a risk of overdose and death. This risk is increased with concurrent abuse of EMBEDA with alcohol and other substances. Taking chewed, crushed, or dissolved EMBEDA enhances drug release and increases the risk of overdose and death. The sequestered naltrexone hydrochloride in EMBEDA is intended to have no clinical effect when EMBEDA is taken as directed; however, if the capsules are crushed or chewed, up to 100% of the sequestered naltrexone HCl dose could be released, bioequivalent to an immediate-release (IR) naltrexone HCl oral solution of the same dose. In opioid-tolerant individuals, the absorption of naltrexone HCl may increase the risk of precipitating withdrawal.

Due to the presence of talc as one of the excipients in EMBEDA, 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.

### Abuse Deterrence Studies

EMBEDA is formulated with a sequestered opioid antagonist, naltrexone HCl, which is released with manipulation by crushing.

### In Vitro Testing

In vitro laboratory tests were performed to evaluate the effect of different physical and chemical conditions intended to defeat the extended-release formulation. When EMBEDA is crushed and mixed in a variety of solvents, both morphine sulfate and naltrexone hydrochloride are simultaneously extracted.

### Clinical Studies

The abuse potential of EMBEDA when crushed was examined in three studies following administration by the oral (Studies 1 and 2) and intranasal (Study 3) routes. A fourth study was conducted with IV administration of simulated crushed EMBEDA (Study 4). These were randomized, double-blind, single-dose, placebo and active-controlled, crossover studies in non-dependent recreational opioid users. Drug Liking in Studies 1- 3 was measured on a bipolar 100-point Visual Analog Scale (VAS) where 0 represents maximum disliking, 50 represents a neutral response (neither like nor dislike), and 100 represents maximum liking. Drug Liking in Study 4 and Drug High in all studies was measured on a unipolar 100-point VAS where 0 represents no response and 100 represents maximum response. Response to whether the subject would take the study drug again was also measured in two studies (Study 2, Study 3) on a bipolar 100-point VAS where 0 represents the strongest negative response (e.g., 'definitely would not'), 50 represents a neutral response, and 100 represents the strongest positive response (e.g., 'definitely would'). The pharmacokinetics of morphine sulfate and naltrexone hydrochloride were also determined in these abuse potential studies. When EMBEDA was crushed and administered by the oral and intranasal routes, morphine and naltrexone were absorbed with similar median time-to-peak concentration ( $T_{max}$ ) values of 1 hour following oral administration and approximately 36 minutes following intranasal administration.

### Oral Studies

Study 1 compared EMBEDA to IR morphine sulfate. In this study 32 subjects received four treatments: 120 mg/4.8 mg as intact EMBEDA capsules, 120 mg/4.8 mg as crushed EMBEDA in solution, 120 mg IR morphine in solution, and placebo. When EMBEDA was crushed and taken orally, the geometric mean ( $\pm$ SD) values for naltrexone  $C_{max}$  and  $AUC_{inf}$  were  $1073 \pm 721$  pg/mL and  $3649 \pm 1868$  pg-hr/mL, respectively. The oral administration of crushed EMBEDA was associated with statistically significantly lower mean and median Drug Liking and Drug High scores compared with crushed IR morphine (as summarized in Table 3).

Figure 1 (Study 1) demonstrates a comparison of Drug Liking for crushed EMBEDA compared to crushed IR morphine sulfate when given by the oral route in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in Drug Liking with crushed EMBEDA vs. morphine greater than or equal to the value on the X-axis. Of the 32 subjects who completed the study, approximately 81% of subjects had some reduction in Drug Liking and Drug High with crushed EMBEDA compared to administration of IR morphine sulfate, while approximately 19% had no reduction in Drug Liking or in Drug High. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to IR morphine was observed in 72% and 56% of subjects, respectively (summarized in Figure 1). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 56% and 31% of subjects, respectively.

Study 2 compared EMBEDA to ER morphine sulfate. In this study 36 subjects were randomized to receive three treatments in solution: 120 mg/4.8 mg as crushed EMBEDA capsules, 120 mg crushed ER morphine, and placebo. When EMBEDA was crushed and taken orally, the geometric mean ( $\pm$ SD) values for naltrexone  $C_{max}$ ,  $AUC_{0-2h}$ , and  $AUC_{inf}$  were  $824 \pm 469$  pg/mL,  $1121 \pm 561$  pg-hr/mL, and  $2984 \pm 1388$  pg-hr/mL, respectively. The oral administration of crushed EMBEDA was associated with statistically significantly lower mean and median Drug Liking, Drug High, and Take Drug Again scores compared with crushed ER morphine (summarized in Table 3).

Figure 1 (Study 2) demonstrates a comparison of maximum Drug Liking for crushed EMBEDA compared to crushed ER morphine in subjects who received both treatments. Of the 33 subjects who completed the study, approximately 85% of subjects had some reduction in Drug Liking with crushed EMBEDA compared to administration of crushed ER morphine sulfate, while approximately 15% had no reduction in Drug Liking. Similarly, 100% of subjects showed some reduction in Drug High with crushed EMBEDA compared to crushed ER morphine. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to crushed

ER morphine was observed in 76% and 52% of subjects, respectively (summarized in Figure 1). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 79% and 64% of subjects, respectively.

**Table 3. Summary of Abuse Potential Maximal Responses ( $E_{max}$ ) with Oral Administration of Crushed EMBEDA Compared to Crushed IR Morphine Sulfate (Study 1) or Crushed ER Morphine (Study 2)**

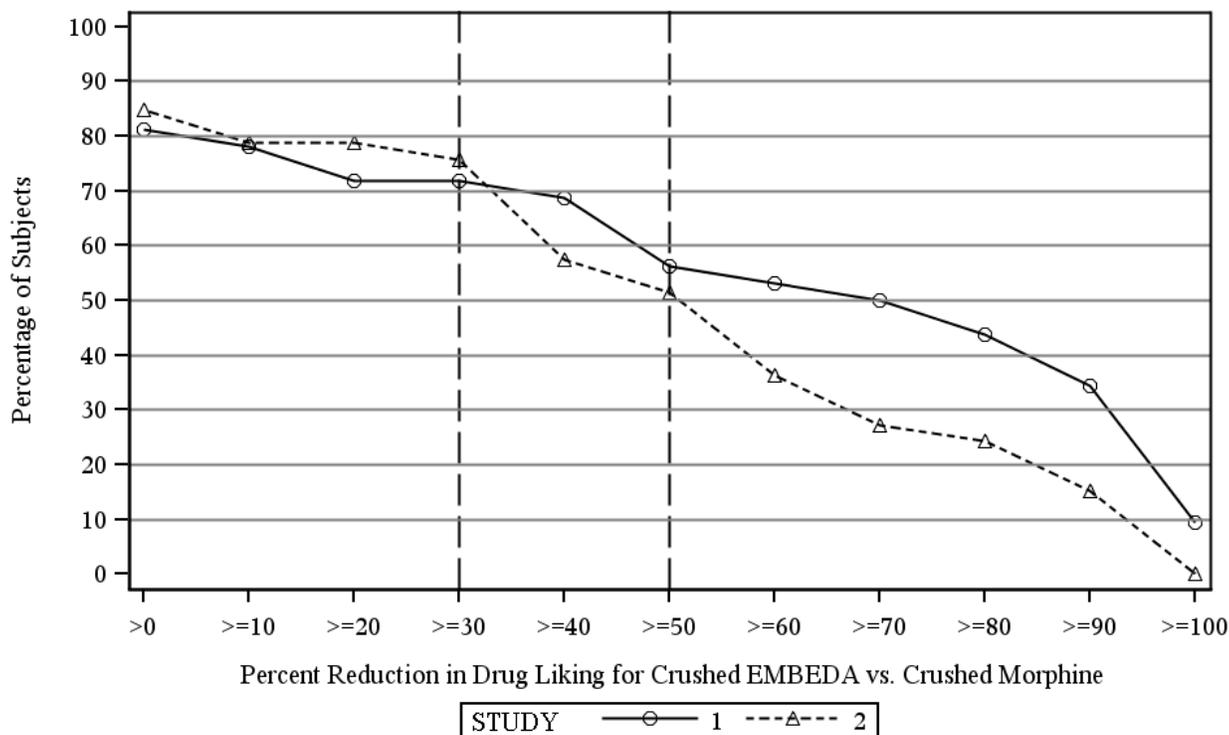
VAS Scale (100 point)		$E_{max}$	
		Crushed EMBEDA (120 mg/4.8 mg)	Crushed Morphine (120 mg)
<b>Study 1</b>			<b>Immediate Release</b>
Drug Liking*	Mean (SE)	68.1 (3.1)	89.5 (2.2)
	Median (range)	62 (50-100)	93 (57-100)
Drug High**	Mean (SE)	54.7 (6.1)	90.2 (2.1)
	Median (range)	64 (0-100)	97 (61-100)
<b>Study 2</b>			<b>Extended Release</b>
Drug Liking*	Mean (SE)	65.2 (2.0)	80.6 (2.3)
	Median (range)	65 (51-100)	81 (50-100)
Drug High**	Mean (SE)	29.2 (3.6)	64.1 (3.3)
	Median (range)	27 (0-78)	63 (28-100)
Take Drug Again*	Mean (SE)	58.0 (3.8)	70.6 (4.3)
	Median (range)	58 (9-100)	75 (12-100)

\* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

\*\*Presented on a unipolar 100-point VAS scale (0=no response, 100=maximum response).

$E_{max}$  = maximal response; ER = extended release; IR = immediate release; SE = standard error.

**Figure 1: Percent Reduction Profiles for  $E_{max}$  of Drug Liking VAS for EMBEDA vs. Morphine Following Oral Administration in Studies 1 and 2.**



#### Intranasal Study

Study 3 compared intranasal administration of crushed EMBEDA to crushed ER morphine sulfate. In this study, 33 subjects were randomized to receive three treatments: 30 mg/1.2 mg as crushed EMBEDA, 30 mg crushed ER morphine, and crushed placebo. When EMBEDA was crushed and taken intranasally, the geometric mean ( $\pm$ SD) values for naltrexone  $C_{max}$ ,  $AUC_{0-2h}$ , and  $AUC_{inf}$  were  $1441 \pm 411$  pg/mL,  $1722 \pm 441$  pg·hr/mL and  $3228 \pm 846$  pg·hr/mL, respectively. Intranasal administration of crushed EMBEDA was

associated with statistically significantly lower mean and median Drug Liking, Drug High, and Take Drug Again scores compared with crushed ER morphine (summarized in Table 4).

Figure 2 demonstrates a comparison of maximum Drug Liking for intranasal administration of crushed EMBEDA compared to crushed ER morphine in subjects who received both treatments. Of the 27 subjects who completed the study, approximately 78% of subjects had some reduction in Drug Liking with crushed EMBEDA compared to administration of crushed ER morphine sulfate, while approximately 22% had no reduction in Drug Liking. Similarly, approximately 70% of subjects showed some reduction in Drug High with crushed EMBEDA compared to crushed ER morphine and approximately 30% of subjects had no reduction in Drug High. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to crushed ER morphine was observed in 63% and 59% of subjects, respectively (summarized in Figure 2). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 59% and 37% of subjects, respectively.

**Table 4. Summary of Abuse Potential Maximal Responses ( $E_{max}$ ) with Intranasal Administration of Crushed EMBEDA Compared to Crushed ER Morphine Sulfate (Study 3)**

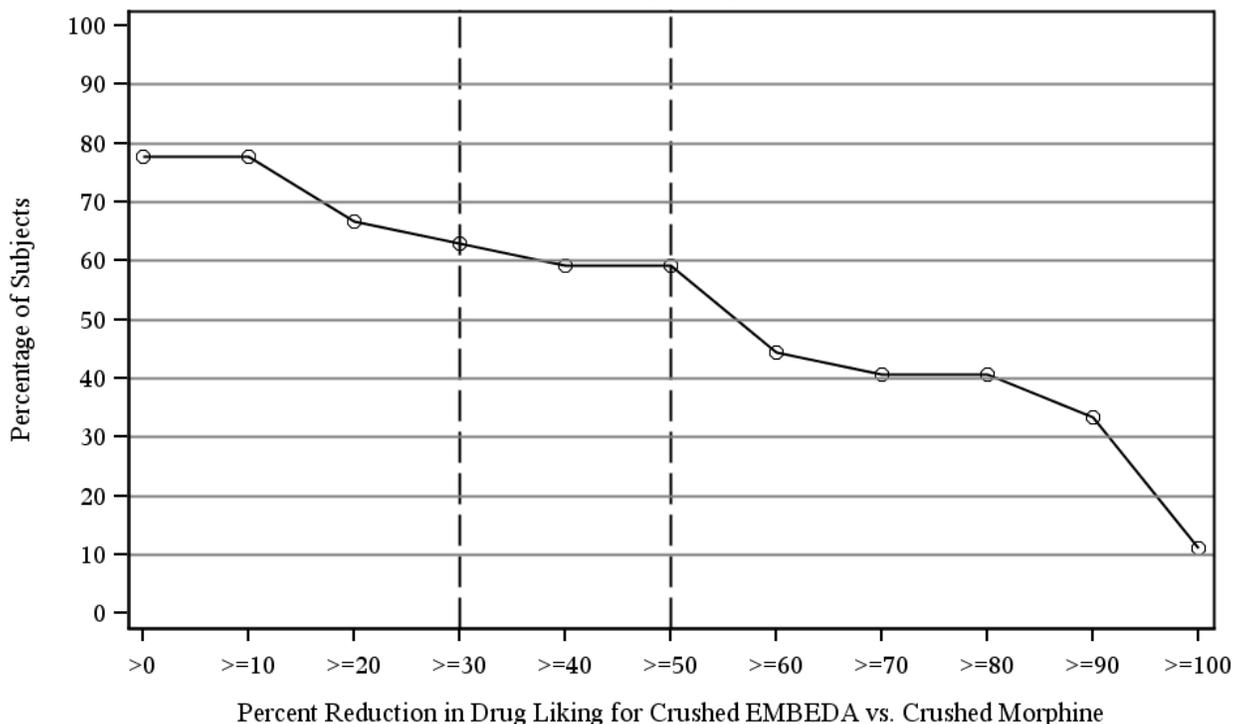
VAS Scale (100 point)		$E_{max}$	
		Crushed EMBEDA (30 mg/1.2 mg)	Crushed ER Morphine (30 mg)
Drug Liking*	Mean (SE)	69.0 (3.5)	88.4 (3.2)
	Median (range)	66 (50-100)	100 (51-100)
Drug High**	Mean (SE)	48.6 (7.8)	84.4 (3.8)
	Median (range)	51 (-39-100)	100 (42-100)
Take Drug Again*	Mean (SE)	59.1 (5.4)	87.0 (4.0)
	Median (range)	56 (0-100)	100 (12-100)

\* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

\*\*Presented on a unipolar 100-point VAS scale (0=no response, 100=maximum response).

$E_{max}$  = maximal response; ER = extended release; SE = standard error.

**Figure 2: Percent Reduction Profiles for  $E_{max}$  of Drug Liking VAS for EMBEDA vs. Morphine Following Intranasal Administration in Study 3.**



*Simulated IV Study*

Study 4, a randomized double-blind, placebo-controlled, three-way cross-over trial in 28 non-dependent recreational opioid users, was performed using 30 mg of intravenous (IV) morphine sulfate alone and 30 mg of IV morphine sulfate in combination with 1.2 mg of

IV naltrexone to simulate parenteral use of crushed EMBEDA. These doses were based on the assumption of the complete release of both morphine sulfate and naltrexone hydrochloride upon crushing EMBEDA. Intravenous administration of the combination of morphine sulfate and naltrexone hydrochloride was associated with statistically significantly lower mean and median Drug Liking and Drug High scores (median scores 34 and 23, respectively) compared with morphine alone (median scores 86 and 89, respectively). Three of the 26 subjects who completed the study had no reduction in Drug Liking and all the subjects showed some reduction in Drug High. Intravenous injection of crushed EMBEDA may result in serious injury and death due to a morphine overdose and may precipitate a severe withdrawal syndrome in opioid-dependent patients.

#### *Summary*

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. These data along with results from the oral and intranasal human abuse potential studies indicate that EMBEDA has properties that are expected to reduce abuse via the oral and intranasal route. However, abuse of EMBEDA by these routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of EMBEDA on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

A human abuse potential study of intravenous morphine and naltrexone to simulate crushed EMBEDA demonstrated lower Drug Liking and Drug High compared with morphine alone. However, it is unknown whether these results with simulated crushed EMBEDA predict a reduction in abuse by the IV route until additional postmarketing data are available.

EMBEDA contains morphine sulfate, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. EMBEDA can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)*].

### **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.

EMBEDA should not be abruptly discontinued [*see Dosage and Administration (2.3)*]. If EMBEDA 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 overdose with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes, 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 patients who are known, or suspected to be, physically dependent on EMBEDA. 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 EMBEDA, carefully monitor the patient until spontaneous respiration is reliably re-established. EMBEDA will continue to release morphine adding to the morphine load for up to 24 hours after administration, necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of an opioid receptor antagonist may precipitate acute withdrawal. The severity of the withdrawal produced 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.

The sequestered naltrexone in EMBEDA has no role in the treatment of opioid overdose.

## 11 DESCRIPTION

EMBEDA extended-release capsules are for oral use and contain pellets of morphine sulfate and naltrexone hydrochloride at a ratio of 100:4. Morphine sulfate is an agonist and naltrexone hydrochloride is an antagonist at the mu-opioid receptor.

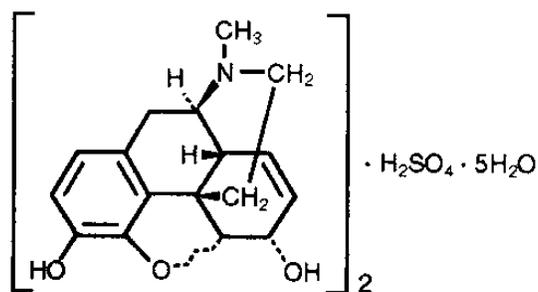
Each EMBEDA extended-release capsule contains the following inactive ingredients common to all strengths: talc, ammonio methacrylate copolymer, sugar spheres, ethylcellulose, sodium chloride, polyethylene glycol, hydroxypropyl cellulose, dibutyl sebacate, methacrylic acid copolymer, diethyl phthalate, magnesium stearate, sodium lauryl sulfate, and ascorbic acid.

The capsule shells contain gelatin, titanium dioxide, and grey ink, FD&C yellow #10 (EMBEDA 20 mg/0.8 mg), FD&C red #3, FD&C blue #1 (EMBEDA 30 mg/1.2 mg), D&C red #28, FD&C red #40, FD&C blue #1 (EMBEDA 50 mg/2 mg), D&C red #28, FD&C red #40, FD&C blue #1 (EMBEDA 60 mg/2.4 mg), FD&C blue #1, FD&C red #40, FD&C yellow #6 (EMBEDA 80 mg/3.2 mg), D&C yellow #10, FD&C blue #1 (EMBEDA 100 mg/4 mg).

### Morphine Sulfate

The chemical name of morphine sulfate is 7,8-didehydro-4,5  $\alpha$ -epoxy-17-methyl-morphinan-3,6  $\alpha$ -diol sulfate (2:1) (salt) pentahydrate. The empirical formula is  $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$  and its molecular weight is 758.85.

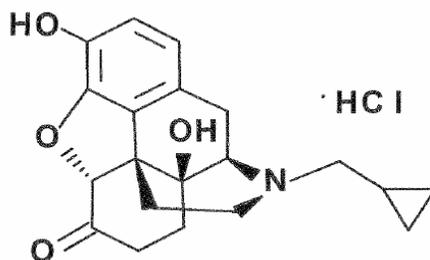
Morphine sulfate is an odorless, white, crystalline powder with a bitter taste. It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol:water partition coefficient of morphine is 1.42 at physiologic pH and the  $pK_b$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



### Naltrexone Hydrochloride

The chemical name of naltrexone hydrochloride is (5 $\alpha$ )-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. The empirical formula is  $C_{20}H_{23}NO_4 \cdot HCl$  and its molecular weight is 377.46.

Naltrexone hydrochloride is a white to slightly off-white powder that is soluble in water. Its structural formula is:



## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### Morphine Sulfate

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 sulfate include dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release, physical dependence, and alterations of the endocrine and autonomic nervous systems.

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 periaqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

#### Naltrexone Hydrochloride

Naltrexone is a centrally acting mu-opioid antagonist that reverses the subjective and analgesic effects of mu-opioid receptor agonists by competitively binding at mu-opioid receptors.

### 12.2 Pharmacodynamics

#### Morphine 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 EMBEDA is used in conjunction with alcohol, other opioids, or illicit drugs that cause CNS depression.

#### Effects on the CNS

The principal actions of therapeutic value of morphine are analgesia and sedation. 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 of analgesic effects. In addition, when morphine binds to mu-opioid receptors, it results in positive subjective effects, such as drug liking, euphoria, and high.

Morphine produces respiratory depression by direct action on brainstem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation. Morphine depresses the cough reflex by direct effect on the cough center in the medulla.

Morphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia in the setting of morphine overdose.

#### Effects on the Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary, and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility 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 is 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

Morphine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Release of histamine may be induced by morphine and can contribute to opioid-induced hypotension. Manifestations of histamine release or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

#### Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (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

##### *Morphine Sulfate*

EMBEDA Capsules contain extended-release pellets of morphine sulfate that release morphine slowly compared to an oral morphine solution. Following the administration of oral morphine solution, approximately 50% of the morphine absorbed reaches the systemic circulation within 30 minutes, compared to 8 hours with an equal amount of EMBEDA. Because of pre-systemic elimination, only about 20 to 40% of the administered dose reaches the systemic circulation.

EMBEDA is bioequivalent to a similarly formulated morphine sulfate extended-release capsules product with regard to rate and extent of plasma morphine absorption. The median time to peak plasma morphine levels ( $T_{max}$ ) was shorter for EMBEDA (7.5 hrs) compared to the comparator (10 hrs). Dose-related increase in steady-state pre-dose plasma concentrations of morphine were noted following multiple-dose administration of EMBEDA in patients.

**Food Effect:** While concurrent administration of high-fat food decreased the rate and extent of morphine absorption from EMBEDA, the total bioavailability was not affected. Co-administration of a high-fat meal with EMBEDA did not compromise the sequestration of naltrexone.

##### *Naltrexone*

Following single dose administration of intact EMBEDA 60/2.4 – 120/4.8 mg, a limited number (~2%) of blood samples had low plasma naltrexone levels (median = 7.74 pg/mL, range 4-132 pg/mL); naltrexone was not detected in the remaining samples. In patients titrated up to 60/2.4–80/3.2 mg EMBEDA twice daily, naltrexone levels (4-26 pg/mL) were detected in 13 out of 67 patients at steady-state. In a long-term safety study where an average dose of EMBEDA was up to 860 mg of morphine administered twice daily for 12 months, 11% of blood samples at pre-dose timepoints at steady-state had detectable plasma naltrexone concentrations ranging from 4 to 145 pg/mL.

Compared to 2.4 mg naltrexone oral solution, which produced mean (SD) naltrexone plasma levels of 689 ( $\pm$  429 pg/mL) and mean (SD) 6 $\beta$ -naltrexol plasma levels of 3920 ( $\pm$  1350 pg/mL), administration of intact 60 mg EMBEDA produced no naltrexone plasma levels and mean (SD) 6 $\beta$ -naltrexol plasma levels of 16.7 ( $\pm$  13.5 pg/mL). Trough levels of plasma naltrexone and 6- $\beta$ -naltrexol did not accumulate upon repeated administration of EMBEDA.

When EMBEDA is crushed or chewed, up to 100% of the sequestered naltrexone dose could be released, bioequivalent to an immediate-release oral solution of the same dose.

#### Distribution

##### *Morphine*

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. The volume of distribution of morphine is approximately 3 to 4 L/kg. Morphine is 30 to 35% reversibly bound to plasma proteins. Although the primary site of action of morphine is in the CNS, only small quantities pass the blood-brain barrier. Morphine also crosses the placental membranes [see *Use in Specific Populations (8.1)*] and has been found in breast milk [see *Use in Specific Populations (8.3)*].

## Metabolism

### *Morphine*

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

### *Naltrexone*

Naltrexone is extensively metabolized into 6- $\beta$ -naltrexol.

## Excretion

### *Morphine*

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 cycling.

The mean adult plasma clearance of morphine is about 20 to 30 mL/minute/kg. The effective half-life of morphine after IV administration is reported to be approximately 2 hours. The terminal elimination half-life of morphine following single dose EMBEDA administration is approximately 29 hours.

## Specific Populations

### *Geriatric Patients*

The pharmacokinetics of EMBEDA have not been investigated in elderly patients (>65 years) although such patients were included in clinical studies. In a long-term open label safety study, the pre-dose plasma morphine concentrations after dose normalization were similar for subjects <65 years and those  $\geq$ 65 years of age.

### *Pediatric Patients*

The pharmacokinetics of EMBEDA have not been evaluated in a pediatric population.

### *Gender*

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

### *Race*

Chinese subjects given IV morphine in one study had a higher clearance when compared to Caucasian subjects ( $1852 \pm 116$  mL/min vs.  $1495 \pm 80$  mL/min).

### *Hepatic Impairment*

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

### *Renal Impairment*

The pharmacokinetics of morphine are altered in patients with renal failure. The AUC is increased and clearance is decreased. Metabolites, M3G and M6G, accumulate several-fold in patients with renal failure compared to healthy subjects. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.

### *Drug Interaction/Alcohol Interaction*

A pharmacokinetic drug interaction is noted with concomitant administration of 40% alcohol and EMBEDA, where an average 2-fold (range 1.4- to 5-fold increase) higher  $C_{max}$  of morphine was noted compared to EMBEDA consumed with water.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

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

#### Mutagenesis

No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic in vitro increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the in vivo

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

#### Impairment of Fertility

No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies, 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, LH, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.

## 14 CLINICAL STUDIES

The analgesic efficacy of EMBEDA has been evaluated in one randomized, double-blind, placebo-controlled clinical trial in osteoarthritis patients with moderate to severe pain (Study ALO-KNT-301). This study, with a randomized withdrawal design, was conducted in subjects with moderate to severe pain from osteoarthritis of the hip or knee over a 12-week treatment period. Subjects started open-label treatment with EMBEDA and titrated to effect. Once their pain was controlled (Brief Pain Inventory [BPI] Average 24-hour Pain Intensity  $\leq 4$  AND at least a 2-point drop from screening baseline), they were randomized to either active treatment with EMBEDA or were tapered off EMBEDA using a double-dummy design and placed on placebo. Of these, 75.1% of the randomized subjects were opioid-naïve and distributed evenly between the 2 groups.

The mean change in the weekly diary BPI average pain score from randomization baseline (Visit Y) to the end of study (Visit Y + 12 Weeks/Early Termination) was statistically significantly superior for those treated with EMBEDA compared to the placebo group.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

	<b>EMBEDA 20 mg/0.8 mg</b>	<b>EMBEDA 30 mg/1.2 mg</b>	<b>EMBEDA 50 mg/2 mg</b>	<b>EMBEDA 60 mg/2.4 mg</b>	<b>EMBEDA 80 mg/3.2 mg</b>	<b>EMBEDA 100 mg/4 mg</b>
<b>Morphine sulfate</b>	20 mg	30 mg	50 mg	60 mg	80 mg	100 mg
<b>Sequestered naltrexone hydrochloride</b>	0.8 mg	1.2 mg	2 mg	2.4 mg	3.2 mg	4 mg
<b>Extended- Release Capsule Description</b> For all strengths, the darker-toned cap has “EMBEDA” printed in grey ink and a single grey band around $\frac{3}{4}$ of the circumference.	Two-toned, yellow opaque hard gelatin capsule. The lighter-toned body has “20” reverse-printed in a grey circle.	Two-toned, blue-violet opaque hard gelatin capsule. The lighter-toned body has “30” reverse-printed in a grey circle.	Two-toned, blue opaque hard gelatin capsule. The lighter-toned body has “50” reverse-printed in a grey circle.	Two-toned, pink opaque hard gelatin capsule. The lighter-toned body has “60” reverse-printed in a grey circle.	Two-toned, light peach opaque elongated hard gelatin capsule. The lighter-toned body has “80” reverse-printed in a grey circle.	Two-toned, green opaque hard gelatin capsule. The lighter-toned body has “100” reverse-printed in a grey circle.
<b>Bottle Size</b>	75 cc	75 cc	75 cc	75 cc	75 cc	75 cc
<b>Bottle Count</b>	30 capsules	30 capsules	30 capsules	30 capsules	30 capsules	30 capsules
<b>NDC #</b>	60793-430-20	60793-431-20	60793-433-20	60793-434-20	60793-435-20	60793-437-20

Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F).

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

## 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 EMBEDA, 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 EMBEDA with others and to take steps to protect EMBEDA 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 EMBEDA 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 EMBEDA securely and to dispose of unused EMBEDA by flushing the capsules down the toilet.

### Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of EMBEDA 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, or prescription and non-prescription products that contain alcohol, during treatment with EMBEDA. The co-ingestion of alcohol with EMBEDA 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 EMBEDA 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 EMBEDA, including the following:

- Swallow EMBEDA capsules whole or sprinkle the capsule contents on applesauce and then swallow immediately without chewing
- Do not crush, chew, or dissolve the pellets contained in the capsules due to a risk of fatal morphine overdose or naltrexone precipitated withdrawal symptoms in opioid-dependent individuals
- Use EMBEDA exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Do not discontinue EMBEDA without first discussing the need for a tapering regimen with the prescriber

### Hypotension

Inform patients that EMBEDA 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 EMBEDA 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 EMBEDA. Advise patients how to recognize such a reaction and when to seek medical attention.

### Pregnancy

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

### Disposal of Unused EMBEDA

Advise patients to flush the unused capsules down the toilet when EMBEDA is no longer needed.

This product's label may have been updated. For current full prescribing information please visit [www.pfizer.com](http://www.pfizer.com).



## Medication Guide

**EMBEDA<sup>®</sup> (im-bed-a)**

**(morphine sulfate and naltrexone hydrochloride) extended-release capsules, CII**

### EMBEDA 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 EMBEDA:

- **Get emergency help right away if you take too much EMBEDA (overdose).** When you first start taking EMBEDA, 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 EMBEDA. They could die from taking it. Store EMBEDA away from children and in a safe place to prevent stealing or abuse. Selling or giving away EMBEDA is against the law.

### Do not take EMBEDA if you have:

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

### Before taking EMBEDA, tell your healthcare provider if you have a history of:

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

### When taking EMBEDA:

- Do not change your dose. Take EMBEDA exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 12 or 24 hours, at the same time every day, as instructed by your healthcare provider. Do not take more than your prescribed daily dose within a 24-hour period. If you miss a dose, take your next dose at your usual time.
- Swallow EMBEDA whole. Do not cut, break, chew, crush, dissolve, snort, or inject EMBEDA because this may cause you to overdose and die.
- You should not receive EMBEDA through a nasogastric tube or gastric tube (stomach tube).
- If you cannot swallow EMBEDA 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 EMBEDA without talking to your healthcare provider.**
- After you stop taking EMBEDA, flush any unused capsules down the toilet.

### While taking EMBEDA DO NOT:

- Drive or operate heavy machinery until you know how EMBEDA affects you. EMBEDA 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 EMBEDA may cause you to overdose and die.

### The possible side effects of EMBEDA 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 EMBEDA. 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](http://dailymed.nlm.nih.gov)**

Manufactured for: Pfizer Inc, New York, NY 10017 by: Actavis Elizabeth LLC, 200 Elmora Avenue, Elizabeth, NJ 07207, [www.embeda.com](http://www.embeda.com) or call 1-800-438-1985

## Instructions For Use EMBEDA® (im-bed-a)

### (morphine sulfate and naltrexone hydrochloride) extended-release Capsules, CII

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

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

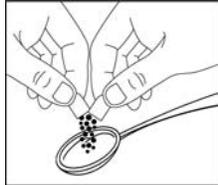


Figure 1

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

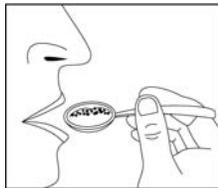


Figure 2

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

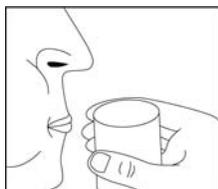


Figure 3

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



Figure 4

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

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

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

Manufactured for: Pfizer Inc, New York, NY 10017  
by: Actavis Elizabeth LLC, 200 Elmora Avenue, Elizabeth, NJ 07207

Revised April 2014

LAB-0631-2.0