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: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, ACCIDENTAL EXPOSURE, and INTERACTION WITH ALCOHOL

See full prescribing information for complete boxed warning.

- **EMBEDA contains pellets of morphine sulfate, a Schedule II controlled substance and a sequestered core of naltrexone hydrochloride. Monitor for signs of misuse, abuse, and addiction during EMBEDA therapy. (5.1, 9)**
- **Fatal respiratory depression may occur, with highest risk at initiation and with dose increases. Instruct patients on proper administration of EMBEDA capsules to reduce the risk. (5.2)**
- **Accidental ingestion of EMBEDA can result in fatal overdose of morphine, especially in children. (5.3)**
- **Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while taking EMBEDA because of the risk of increased, and potentially fatal, plasma morphine levels. (5.4)**

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

Boxed Warning	7/2012
Indications and Usage (1)	7/2012
Dosage and Administration (2)	7/2012
Contraindications (4)	7/2012
Warnings and Precautions (5)	7/2012

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

EMBEDA is a combination opioid agonist/opioid antagonist product, indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

Limitations of Use

- EMBEDA is not for use:
  - As an as-needed (prn) analgesic (1)
  - For pain that is mild or not expected to persist for an extended period of time (1)
  - For acute pain (1)
  - For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1)
- EMBEDA 100 mg/4 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. (1)

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

- Individualize dosing based on patient's prior analgesic treatment experience, and titrate as needed to provide adequate analgesia and minimize adverse reactions. (2.1, 2.2, 2.3)
- Instruct patients to swallow EMBEDA capsules intact, or to sprinkle the capsule contents on applesauce and immediately swallow without chewing. (2.4)
- Do not abruptly discontinue EMBEDA in a physically dependent patient. (2.3, 5.12)

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

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

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

- Elderly, cachectic, and debilitated patients and patients with chronic pulmonary disease: Monitor closely because of increased risk of respiratory depression. (5.5, 5.6)
- Interaction with CNS depressants: Consider dose reduction of one or both drugs because of additive effects. (5.7, 7.2)
- Hypotensive effect: Monitor during dose initiation and titration (5.8)
- 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_2 retention. (5.9)

----------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

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

- Mixed agonist/antagonist opioid analgesics: Avoid use with EMBEDA because they may reduce analgesic effect of EMBEDA or precipitate withdrawal symptoms. (5.12, 7.3)
- Muscle relaxants: Avoid use with EMBEDA because of increased risk of respiratory depression. (7.4)
- 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: 11/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, ACCIDENTAL EXPOSURE, and INTERACTION WITH ALCOHOL

Abuse Potential
EMBEDA® contains pellets of morphine sulfate, an opioid agonist, with a sequestered core of naltrexone hydrochloride, an opioid receptor antagonist. Morphine sulfate is a Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit *[see Warnings and Precautions (5.1)]*. Assess each patient's risk for opioid abuse or addiction prior to prescribing EMBEDA. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving EMBEDA for signs of misuse, abuse, and addiction during treatment *[see Drug Abuse and Dependence (9)]*.

Life-threatening Respiratory Depression
Respiratory depression, including fatal cases, may occur with use of EMBEDA, even when the drug has been used as recommended and not misused or abused *[see Warnings and Precautions (5.2)]*. Proper dosing and titration are essential and EMBEDA should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. 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, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine.

Accidental Exposure
Accidental ingestion of EMBEDA, especially in children, can result in a fatal overdose of morphine *[see Warnings and Precautions (5.3)]*.

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

1 INDICATIONS AND USAGE

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

Limitations of Use
EMBEDA is not for use:

- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

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 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 for a week or longer.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

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

Consider the following factors when selecting an initial dose of EMBEDA:

- Total daily dose, potency, and any prior opioid the patient has been taking previously;
- Reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed (Note: potency estimates may vary with the route of administration);
- Patient's degree of opioid experience and opioid tolerance;

- General condition and medical status of the patient;
- Concurrent medication;
- Type and severity of the patient's pain.

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 EMBEDA therapy with the 20 mg/0.8 mg capsule.

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
While there are useful tables of oral and parenteral equivalents, there is substantial inter-patient variation in the relative potency of different opioid drugs and formulations. 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. 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 Sulfate: Specific recommendations are not available because of a lack of systematic evidence for these types of analgesic substitutions. Published relative potency data are available, but such ratios are approximations. In general, begin with half of the estimated daily morphine requirement as the initial dose, managing inadequate analgesia by supplementation with immediate-release morphine.

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 at a frequency of either once or twice daily. Continually reevaluate patients receiving EMBEDA to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), periodically reassess the continued need for the use of 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 dosage adjustments may be done every 1 to 2 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with a small dose of an immediate-release medication. In patients experiencing inadequate analgesia with once daily dosing of EMBEDA, consider a twice daily regimen.

If signs of excessive opioid-related adverse reactions are observed, the next dose 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 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 tubes.

3 DOSAGE FORMS AND STRENGTHS

EMBEDA contains 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 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 ¾ of the circumference. The lighter-toned body has "20" reverse-printed in a grey circle.

Each 30 mg/1.2 mg 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 ¾ of the circumference. The lighter-toned body has "30" reverse-printed in a grey circle.

Each 50 mg/2 mg 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 ¾ of the circumference. The lighter-toned body has "50" reverse-printed in a grey circle.

Each 60 mg/2.4 mg 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 ¾ of the circumference. The lighter-toned body has "60" reverse-printed in a grey circle.

Each 80 mg/3.2 mg 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 ¾ of the circumference. The lighter-toned body has "80" reverse-printed in a grey circle.

Each 100 mg/4 mg 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 ¾ 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 Abuse Potential

EMBEDA contains morphine, an opioid agonist and a Schedule II controlled substance. Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing EMBEDA in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient's risk for opioid abuse or addiction prior to prescribing EMBEDA. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of EMBEDA by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could 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 (5.12)]*.

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

Respiratory depression is the primary risk of EMBEDA. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. 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)]*.

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. Instruct patients against use by individuals other than the patient for whom EMBEDA was prescribed and to keep EMBEDA out of the reach of children, as such inappropriate use may result in fatal respiratory depression.

To reduce the risk of respiratory depression, proper dosing and titration of EMBEDA are essential *[see Dosage and Administration (2.2, 2.3)]*. Overestimating the EMBEDA dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused.

To further reduce the risk of respiratory depression, consider the following:

- Proper dosing and titration are essential and EMBEDA should only be prescribed 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 for use in opioid-tolerant patients only. Ingestion of this strength of EMBEDA capsules or of the pellets within the capsule may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.
- Instruct patients to swallow EMBEDA capsules intact or to sprinkle the capsule contents on applesauce and swallow immediately without chewing. The pellets in the capsules are not to be crushed, dissolved, or chewed. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals.
- EMBEDA is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression *[see Contraindications (4)]*.

5.3 Accidental Exposure

Accidental ingestion of EMBEDA, especially in children, can result in a fatal overdose of morphine.

5.4 Interaction with Alcohol

The co-ingestion 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)]*.

5.5 Elderly, Cachectic, and Debilitated Patients

Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance compared to younger, healthier patients. Therefore, 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 Interactions with CNS Depressants and Illicit Drugs

Hypotension, profound sedation, coma, or respiratory depression may result if EMBEDA is used concomitantly with other 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, consider the patient's use, if any, of alcohol or illicit drugs that cause CNS depression. If EMBEDA therapy is to be initiated in a patient taking a CNS depressant, start with a lower EMBEDA dose than usual and 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)]*.

5.8 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.

5.9 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking EMBEDA who may be susceptible to the intracranial effects of CO_2 retention (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_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

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

5.10 Use in Patients with Gastrointestinal Conditions

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

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

5.11 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.

5.12 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including EMBEDA. In these patients, mixed agonists/antagonists 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 fluid administration.

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

5.13 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.

5.14 Interference with Laboratory Tests

Naltrexone does not interfere with thin-layer, gas-liquid, and high pressure 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 and/or conditions are discussed elsewhere in the labeling:

- Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Chronic Pulmonary Disease *[see Warnings and Precautions (5.6)]*
- Head Injuries and Increased Intracranial Pressure *[see Warnings and Precautions (5.9)]*
- Interactions with Other CNS Depressants *[see Warnings and Precautions (5.7)]*
- Hypotensive Effect *[see Warnings and Precautions (5.8)*
- Gastrointestinal Effects *[see Warnings and Precautions (5.10)*
- Seizures *[see Warnings and Precautions (5.11)*

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 (may be severe), vomiting, fatigue, dizziness, pruritus, and somnolence.

6.1 Clinical Studies 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 ≥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 ≥2% of Subjects in the Randomized Study

	Titration	Maintenance	
Adverse Reaction	**EMBEDA (N=547) n (%)[1=]**	**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 ≥ 2.0% of subjects are presented in Table 2.

Table 2: Adverse Reactions Reported by ≥ 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 (≥10%): constipation, nausea, somnolence

Common (≥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

Concurrent use of EMBEDA and other central nervous system (CNS) depressants (e.g. sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, and

profound sedation or coma. Monitor patients receiving CNS depressants and EMBEDA for signs of respiratory depression and hypotension. When such combined therapy is contemplated, reduce the initial dose of one or both agents

7.3 Mixed Agonist/Antagonist Opioid Analgesics

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

7.4 Muscle Relaxants

Opioids may enhance the neuromuscular blocking action of skeletal 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 (PGP) Inhibitors

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects (Pregnancy Category C)
No formal studies to assess the teratogenic effects of morphine in animals have been conducted. It is also not known whether morphine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Morphine should be given to a pregnant woman only if clearly needed.

In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

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

toxicity was observed in this study, however, increased mortality and growth retardation were seen in the offspring. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.

Nonteratogenic Effects
Infants born to mothers who have taken opioids chronically may exhibit neonatal withdrawal syndrome *[see Use in Specific Populations (8.6)]*, reversible reduction in brain volume, small size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

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

8.2 Labor and Delivery

EMBEDA is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor by temporarily reducing the strength, duration, and frequency of uterine contractions. However, these effects are not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. An opioid antagonist, such as naloxone, should be available for reversal of opioid-induced respiratory depression in the neonate in such situations.

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)]*.

8.6 Neonatal Opioid Withdrawal Syndrome

Chronic maternal use of morphine during pregnancy can affect the fetus with subsequent withdrawal signs. Neonatal 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 withdrawal syndrome vary based on the drug used, duration of use, the dose of last maternal use, and rate of elimination drug by the newborn. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts.

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 a physical withdrawal.

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

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

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 cut, broken, chewed, crushed, or dissolved EMBEDA enhances drug release and increases the risk of over dose and death. In opioid-tolerant individuals, the absorption of naltrexone may increase the risk of precipitating withdrawal. The sequestered naltrexone 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 dose could be released, bioequivalent to an immediate-release naltrexone oral solution of the same dose.

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.

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, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine). 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, 8.6)*].

10 OVERDOSAGE

Clinical Presentation
Acute overdosage with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, 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 an 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

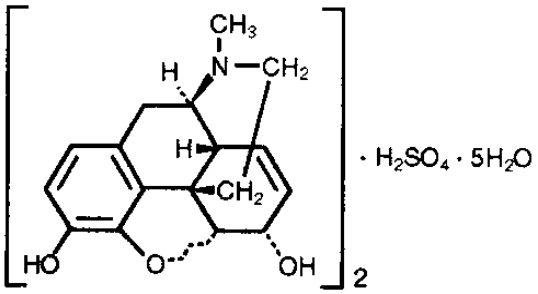
EMBEDA capsules are for oral use and contain pellets of morphine sulfate and naltrexone hydrochloride at a ratio of 100:4. Morphine sulfate is an agonist and naltrexone hydrochloride is an antagonist at the mu-opioid receptor.

Each EMBEDA 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).

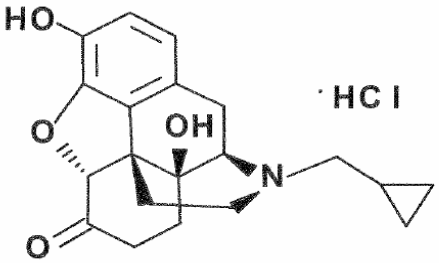
Morphine Sulfate
The chemical name of morphine sulfate is 7,8-didehydro-4,5 α-epoxy-17-methyl-morphinan-3,6 α-diol sulfate (2:1) (salt) pentahydrate. The empirical formula is $(C_{17}H_{19}NO_3)_2 \bullet H_2SO_4 \bullet 5H_2O$ and its molecular weight is 758.85.

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 (5α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. The empirical formula is $C_{20}H_{23}NO_4$•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 analgesia, 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 peri-aqueductal 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 central nervous system depression.

Effects on the Central Nervous System
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 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.

Naltrexone Effect
The pharmacodynamic effect of naltrexone in the setting of crushed EMBEDA was examined in two studies. The clinical significance of the degree of reduction in drug liking and euphoria reported in these studies has not yet been established. There is no evidence that the naltrexone in EMBEDA reduces the abuse liability of EMBEDA.

In a randomized double-blind, triple-dummy, four-way cross-over study, 32 non-dependent recreational opioid users received 120 mg morphine as intact EMBEDA capsules, 120 mg of morphine as crushed EMBEDA capsules, 120 mg of immediate-release (IR) morphine sulfate and placebo. Following administration of crushed EMBEDA, 87.5% of subjects had some degree of reduced drug liking compared to findings following administration of IR morphine sulfate, while 12.5% had no reduction in drug liking. There was considerable individual variability in the degree of reduction in drug liking, ranging between 10 and 50%. Similarly, 69% of subjects showed some degree of a decrease in euphoria with crushed EMBEDA compared to IR morphine sulfate and 31% of subjects did not report a reduction in euphoria. There was similar individual variability in the degree of reduction in euphoria.

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. The combination of morphine with naltrexone resulted in 71% of subjects reporting a reduction in euphoria compared to morphine alone. 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.

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 (± 429 pg/mL) and mean (SD) 6β-naltrexol plasma levels of 3920 (± 1350 pg/mL), administration of intact 60 mg EMBEDA produced no naltrexone plasma levels and mean (SD) 6β-naltrexol plasma levels of 16.7 (± 13.5 pg/mL). Trough levels of plasma naltrexone and 6-β-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-β-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.

Special 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 ≥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 intravenous morphine in one study had a higher clearance when compared to Caucasian subjects (1852 $\pm$ 116 mL/min versus 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 patients with in 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, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.

14 CLINICAL STUDIES

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 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

	EMBEDA 20 mg/0.8 mg	EMBEDA 30 mg/1.2 mg	EMBEDA 50 mg/2 mg	EMBEDA 60 mg/2.4 mg	EMBEDA 80 mg/3.2 mg	EMBEDA 100 mg/4 mg
Morphine sulfate	20 mg	30 mg	50 mg	60 mg	80 mg	100 mg
Sequestered naltrexone hydrochloride	0.8 mg	1.2 mg	2 mg	2.4 mg	3.2 mg	4 mg
Capsule Description For all strengths, the darker-toned cap has "EMBEDA" printed in grey ink and a single grey band around ¾ 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.
Bottle Size	75 cc	75 cc	75 cc	75 cc	75 cc	75 cc
Bottle Count	30 capsules	30 capsules	30 capsules	30 capsules	30 capsules	30 capsules
NDC #	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

See FDA-approved patient labeling (Medication Guide)

Abuse Potential
Inform patients that EMBEDA contains morphine, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share EMBEDA with others and to take steps to protect EMBEDA from theft or misuse.

Life-threatening Respiratory Depression
Discuss the risk of respiratory depression with patients, explaining that the risk is greatest when starting EMBEDA or when the dose is increased. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Exposure
Instruct patients to take steps to store EMBEDA securely. Accidental exposure, especially in children, may results in serious harm or death. Advise patients to dispose of unused EMBEDA by flushing the capsules down the toilet.

Risks from Concomitant Use of Alcohol and other CNS Depressants
Inform patients that the concomitant use of alcohol with EMBEDA can increase the risk of life-threatening respiratory depression. Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter drug products that contain alcohol, during treatment with EMBEDA.

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

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

- Swallowing EMBEDA capsules whole or sprinkling the capsule contents on applesauce and then swallowing immediately without chewing
- Not crushing, chewing, or dissolving the pellets in the capsules due to a risk of fatal morphine overdose or naltrexone precipitated withdrawal symptoms in opioid-dependent individuals
- Using EMBEDA exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Not discontinuing 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.

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

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