INDICATIONS AND USAGE

EMBEDA® (morphine sulfate and naltrexone hydrochloride) extended-release capsules, for oral use, CII

Limitations of Use

alternative treatment options are inadequate. (1)

of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which EMBEDA is a combination opioid agonist/opioid antagonist product indicated for the management

Warnings and Precautions (5.2)

Boxed Warning

RECENT MAJOR CHANGES

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

Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue EMBEDA if serotonin syndrome is suspected. (7)

Mixed Agonist/Agonist and Partial Agonist Opioid Analgesics: Avoid use with EMBEDA because they may reduce analgesic effect of EMBEDA or precipitate withdrawal symptoms. (5.13, 7)

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause fetal harm. (8.1)

Lactation: Not recommended. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2018

ADVERSE REACTIONS

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.6)

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)

Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of EMBEDA in patients with circulatory shock. (5.9)

Risk of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of EMBEDA in patients with impaired consciousness or coma. (5.10)

WARNINGS AND PRECAUTIONS

• Significant respiratory depression (4)
• Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4)
• Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (5.7)
• Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
• Hypersensitivity to morphine or naltrexone (4)

INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

• Significant respiratory depression
• Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
• Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days
• Known or suspected gastrointestinal obstruction, including paralytic ileus
• Hypersensitivity to morphine or naltrexone

Dosage Forms and Strengths

EMBEDA 100 mg/4 mg capsules, a single dose greater than 60 mg/2.4 mg, or a total daily dose greater than 120 mg/5 mg are only for patients in whom tolerance to an opioid of comparable potency is established. (2.1)
WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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* Sections or subsections omitted from the full prescribing information are not listed.
It is safer to underestimate a patient's 24-hour oral morphine dosage and provide rescue medication (e.g., immediate-release morphine) than to overestimate the 24-hour morphine dosage and manage an adverse reaction due to an overdose. While there are useful tables of opioid equivalents readily available, there is inter-patient variability in the relative potency of opioid drugs and opioid formulations.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal and for signs of over sedation/toxicity after converting patients to EMBEDA.

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 areapproximations. 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.

2.3 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 [see Warnings and Precautions (5.1)]. 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.

Patients who experience breakthrough pain may require a dosage adjustment 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 dosage. In patients experiencing inadequate analgesia with once-daily dosing of EMBEDA, consider a twice-daily regimen. Because steady-state plasma concentrations are approximated within 24 to 36 hours, EMBEDA dose may be adjusted every 1 to 2 days.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage.

Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 Dosage Modifications with Concomitant Use of Central Nervous System Depressants

If the patient is currently taking a central nervous system (CNS) depressant and the decision is made to begin EMBEDA, start with 1/2 to 1/2 the recommended starting dosage of EMBEDA, monitor patients for signs of respiratory depression, sedation, and hypotension, and consider using a lower dosage of the concomitant CNS depressant [see Warnings and Precautions (5.5), Drug Interactions (7)].

2.5 Discontinuation of EMBEDA

When a patient no longer requires therapy with EMBEDA, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue EMBEDA [see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.3)].

2.6 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 (5.1)]. 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 (5.13)].

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

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. EMBEDA capsules contain creamy white to light tan spheroidal pellets, have an outer opaque capsule with colors as identified below.

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Morphine Sulfate</th>
<th>Naltrexone Hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMBEDA 20 mg/0.8 mg</td>
<td>20 mg</td>
<td>0.8 mg</td>
</tr>
<tr>
<td>EMBEDA 30 mg/1.2 mg</td>
<td>30 mg</td>
<td>1.2 mg</td>
</tr>
<tr>
<td>EMBEDA 50 mg/2 mg</td>
<td>50 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>EMBEDA 60 mg/2.4 mg</td>
<td>60 mg</td>
<td>2.4 mg</td>
</tr>
<tr>
<td>EMBEDA 80 mg/3.2 mg</td>
<td>80 mg</td>
<td>3.2 mg</td>
</tr>
<tr>
<td>EMBEDA 100 mg/4 mg</td>
<td>100 mg</td>
<td>4 mg</td>
</tr>
</tbody>
</table>

Sequestered naltrexone hydrochloride:
- 0.8 mg
- 1.2 mg
- 2 mg
- 2.4 mg
- 3.2 mg
- 4 mg

4 CONTRAINDICATIONS

EMBEDA is contraindicated in patients with:

- Significant respiratory depression [see Warnings and Precautions (5.3)]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see Warnings and Precautions (5.6)]
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days [see Warnings and Precautions (5.7)]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see Warnings and Precautions (5.7)]
- Hypersensitivity (e.g., anaphylaxis) to morphine or naltrexone [see Adverse Reactions (6.2)]

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)]. Because extended-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 [see Drug Abuse and Dependence (9)].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed EMBEDA. EMBEDA 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 and conditions. Risks are 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). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids 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 (5.13)].

Opioids 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 deal with diversion or misuse of this product.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (e.g., CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide to know how the drug works and to understand common side effects such as constipation and drowsiness, which may require patient education or counseling.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.
5.3 Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, 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 (CO₂) retention from opioid-induced respiratory depression can result in ventilation and perfusion abnormalities that can further reduce cardiac output and blood pressure. Avoid the use of EMBEDA in patients with circulatory shock.

5.10 In Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
In patients susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), EMBEDA may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with EMBEDA.

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.

5.11 Risks of Use in Patients with Gastrointestinal Conditions
EMBEDA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The morphine in EMBEDA may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders
The morphine in EMBEDA may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during EMBEDA therapy.

5.13 Withdrawal
Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who have received or are receiving a full opioid agonist for an extended period of time. These patients may be at risk for mixed agonist/antagonist- and partial agonist-mediated respiratory depression. In the absence of specific antagonist treatment, the respiratory depression may be reversed with the use of an opioid antagonist. The morphine in EMBEDA may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

Consuming EMBEDA capsules that have been altered by chewing, dissolving, or swallowing 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, can last for up to 48 hours, and can include mental status changes, restlessness, lacrimation, rhinorrhea, yawning, perspiration, shakiness, and sweating. Significant fluid losses from vomiting and diarrhea can require intravenous (IV) fluid administration.

When discontinuing EMBEDA, gradually taper the dosage [see Dosage and Administration (2.5)]. Do not abruptly discontinue EMBEDA [see Drug Abuse and Dependence (9.3)].

5.14 Risks of 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 [see Patient Counseling Information (17)].

5.15 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 described, or described in greater detail, in other sections are:

Addiction, Abuse, and Misuse [see Warnings and Precautions (5.1)]

Interactions with Benzodiazepine or Other CNS Depressants [see Warnings and Precautions (5.3)]

Severe Hypotension [see Warnings and Precautions (5.7)]

Adrenal Insufficiency [see Warnings and Precautions (5.8)]

Severe Hypotension [see Warnings and Precautions (5.9)]

Gastrointestinal Adverse Reactions [see Warnings and Precautions (5.11)]

Seizures [see Warnings and Precautions (5.12)]

Withdrawal [see Warnings and Precautions (5.13)]

6.1 Clinical Trials 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.

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

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. In these patients, mixed agonist/antagonist EMBEDA can result in significant withdrawal symptomatology that may further reduce cardiac output and blood pressure. Avoid the use of EMBEDA in patients with circulatory shock.
Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often been reported during concomitant use of opioids with serotonergic drugs.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported voluntarily from a population of uncertain size, it is not always possible to eliminate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post-approval use of morphine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

### Table 1: Adverse Reactions Reported in ≥2% of Subjects in the Randomized Study

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

### Table 2: Adverse Reactions Reported by ≥2.0% of Subjects in Long-Term Safety Study

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

### Table 3: Clinically Significant Drug Interactions with EMBEDA

#### Alcohol

**Clinical Impact:** Concomitant use of alcohol with EMBEDA can result in an increase of morphine plasma levels and potentially fatal overdose of morphine.

**Intervention:** Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on EMBEDA therapy [see Warnings and Precautions (5.5), Clinical Pharmacology (12.2)].

#### Benzodiazepines and Other Central Nervous System (CNS) Depressants

**Clinical Impact:** Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

**Intervention:** Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Dosage and Administration (2.4) and Warnings and Precautions (5.5)].

**Examples:** Benzodiazepines, and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

#### Serotonergic Drugs

**Clinical Impact:** The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

**Intervention:** If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue EMBEDA if serotonin syndrome is suspected.

**Examples:** Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

#### Monoamine Oxidase Inhibitors (MAOIs)

**Clinical Impact:** MAO interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see Warnings and Precautions (5.7)].

**Intervention:** Do not use EMBEDA in patients taking MAOIs or within 14 days of stopping such treatment.

**Examples:** Phenelzine, tranylcypromine, linezolid

#### Mixed Agonist/Agonist and Partial Agonist Opioid Analgesics

**Clinical Impact:** May reduce the analgesic effect of EMBEDA and/or precipitate withdrawal symptoms.

**Intervention:** Avoid concomitant use.

**Examples:** Butorphanol, nalbuphine, pentazocine, buprenorphine

#### Muscle Relaxants

**Clinical Impact:** Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

**Intervention:** Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of EMBEDA and/or muscle relaxant as necessary.

#### Cimetidine

**Clinical Impact:** The concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma, and death.

**Intervention:** Monitor patients for respiratory depression that may be greater than otherwise expected and decrease the dosage of EMBEDA and/or cimetidine as necessary.

#### Diuretics

**Clinical Impact:** Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

**Intervention:** Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

#### Anticholinergic Drugs

**Clinical Impact:** The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

**Intervention:** Monitor patients for signs of urinary retention or reduced gastric motility when EMBEDA is used concomitantly with anticholinergic drugs.

#### P-Glycoprotein (PGP) Inhibitors

**Clinical Impact:** The concomitant use of PGP-inhibitors can increase the exposure of morphine by about two-fold and can increase risk of hypotension, respiratory depression, profound sedation, coma, and death.

**Intervention:** Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of EMBEDA and/or PGP-inhibitor as necessary.
mice at 1 mg/kg or higher (0.08 times the HDD) and rats at 1.5 mg/kg/day or higher (0.2 times the HDD); and a host of behavioral abnormalities in the offspring of rats, including altered responsiveness to opioids at 4 mg/kg/day (0.7 times the HDD) or greater.

Fetal and/or postnatal exposure to morphine in mice and rats has been shown to result in morphological changes in fetal and neonatal neural cell loss, alteration of a number of neurotransmitter and neuromodulator systems, including opioid and non-opioid systems, and impairment in various learning and memory tests that appear to persist into adulthood. These studies were conducted with morphine treatment usually in the range of 4 to 20 mg/kg/day (0.7 to 3.2 times the HDD).

Additionally, delayed sexual maturation and decreased sexual behaviors in female offspring at 20 mg/kg/day (3.2 times the HDD), 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 at 20 mg/kg/day (3.2 times the HDD). Decreased litter size and viability were observed in the offspring of male rats that were intraperitoneally administered morphine sulfate for 1 day prior to mating at 25 mg/kg/day (4.1 times the HDD) and mated to untreated females. Decreased viability and body weight and/or movement deficits in both first and second generation offspring were reported when male mice were treated with 10 mg/kg/day morphine sulfate (9.7 to 19.5 times the HDD) or when female mice were treated with escalating doses of 60 to 240 mg/kg/day (4.9 to 19.5 times the HDD) followed by a 5-day treatment-free recovery period prior to mating. Similar multigenerational findings were also seen in female rats pre-gestationally treated with escalating doses of 10 to 22 mg/kg/day morphine (1.6 to 3.8 times the HDD).

8.2 Lactation

Morphine is present in breast milk. Published lactation studies report variable concentrations of morphine in breast milk with administration of immediate-release morphine to nursing mothers in the early postpartum period with a milk-to-plasma morphine AUC ratio of 2.5:1 measured in one lactation study. However, there is insufficient information to determine the effects of morphine on the breastfed infant and the effects of morphine on milk production. Lactation studies have not been conducted with extended-release morphine, including EMBEDA. Because of the potential for serious adverse reactions in nursing infants from exposure to opioids at 4 mg/kg/day or greater, including respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with EMBEDA.

Clinical Considerations

Monitor infants exposed to EMBEDA through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of morphine is stopped, or when breastfeeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2), Clinical Pharmacology (12.2)].

In published animal studies, morphine administration adversely affected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats [see Nonclinical Toxicology (12.1)].

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 (≥ 65 years) subjects, and such studies were not 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)].

Elderly patients (aged 65 years or older) may have increased sensitivity to EMBEDA. In general, use caution when choosing a dosage for an elderly patient, especially starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titate the dosage of EMBEDA slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see Warnings and Precautions (5.6)].

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Start these patients with a lower than usual dosage of EMBEDA and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension [see Clinical Pharmacology (12.3)].

8.7 Renal Impairment
Morphine pharmacokinetics are altered in patients with renal failure. Start these patients with a lower than usual dosage of EMBEDA and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension [see Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

EMBEDA contains morphine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone, and tapentadol, 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. All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Prescription drug abuse is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persistence of use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical dependence.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “losses” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). “Drug-seeking” (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 an appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers 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 and federal 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 limit 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 central nervous system depressants. Taking cut, broken, 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, embolism and death, 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 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 (\(C_{\text{max}}\)) values of 1 hour following oral administration and approximately 35 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 (±SD) values for naltrexone \(C_{\text{max}}\) and AUC\(_{\text{inf}}\) were 1073 ± 721 pg/mL and 3649 ± 1889 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 4).

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 (±SD) values for naltrexone \(C_{\text{max}}\), AUC\(_{24}\), and AUC\(_{0-24}\) were 824 ± 469 pg/mL, 1121 ± 561 pg·hr/mL, and 2984 ± 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 4).

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 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.

**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 placebo. When EMBEDA was crushed and taken intranasally, the geometric mean (±SD) values for naltrexone \(C_{\text{max}}\), AUC\(_{24}\), and AUC\(_{0-24}\) were 1441 ± 411 pg/mL, 1722 ± 441 pg·hr/mL and 3228 ± 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 5).

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 76% 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.
Figure 2: Percent Reduction Profiles for Emax of Drug Liking VAS for EMBEDA vs. Morphine Following Intranasal Administration in Study 3.

9.3 Dependence

Dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. Dependence may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects. Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with EMBEDA can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations. See Clinical Pharmacology (12.2).

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and 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 nalbuphine, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of morphine in EMBEDA, carefully monitor the patient until spontaneous respiration is reliably reestablished. EMBEDA will continue to release morphine and add to the morphine load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or only brief in nature, administer additional antagonist as directed in the product’s prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist may precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced 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 initiated with care and by titration with smaller than usual doses of the antagonist.

The sequenced naloxone 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 opioid agonist and naltrexone hydrochloride is an opioid antagonist.

Each EMBEDA extended-release capsule contains the following inactive ingredients common to all strengths: talc, ammonium 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 100 mg/4 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 20 mg/0.8 mg), D&C red #28, 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 #9 (EMBEDA 40 mg/1.6 mg), FD&C yellow #10, FD&C blue #1 (EMBEDA 100 mg/4 mg).

Morphine Sulfate

The chemical name of morphine sulfate is 7,8-didehydro-4,5α,6α-dihydroxymorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate. The empirical formula is C20H23NO4•HCl•H2SO4•5H2O 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 physiological pH and the pKa is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4). Its structural formula is:

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Naltrexone Hydrochloride

The chemical name of naltrexone hydrochloride is (5α)-17-(cyclopropylmethy1)-4,5α-epoxy-3,14-dihydroxy morphinan-6-one hydrochloride. The empirical formula is C20H23NO4•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:

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12.1 Mechanism of Action

Morphine Sufate

Morphine is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of morphine is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with morphine. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous opioids and opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Naltrexone Hydrochloride

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

12.2 Pharmacodynamics

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 Central Nervous System

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 both increases in carbon dioxide tension and electrical stimulation.

Morphine causes miosis, even in total darkness. 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 hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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 peristaltic waves are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see Adverse Reactions (6.2)]. 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 androgen deficiency that may manifest as sexual dysfunction and osteoporosis. These effects are usually reversible upon discontinuation of therapy. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various contributing factors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see Adverse Reactions (6.2)].

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of morphine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see Dosage and Administration (2.1, 2.2, 2.3)].

Concentration-Adverse Reaction Relationships

There is a relationship between increasing morphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see Dosage and Administration (2.1, 2.2, 2.3)].

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 (Tmax) was 7.5 hours 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.

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 mg EMBEDA twice daily, naltrexone levels (~29 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 naltrexone 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) 6-naltrexol plasma levels of 3920 ± 1350 pg/mL, administration of intact 60 mg EMBEDA produced no naltrexone plasma levels and mean (SD) 6-naltrexol plasma levels of 16.7 ± 13.5 pg/mL. Trough levels of plasma naltrexone and 6-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.

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.

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 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)].

Elimination

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-sulfate. A small fraction (less than 5%) of morphine is demethylated. M6G 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.

Specific Populations

Age: Geriatric Population

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.

Sex

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

Race/Ethnicity

Chinese subjects given IV morphine in one study had a higher clearance when compared to Caucasian subjects (1852 ± 116 mL/min vs. 1495 ± 80 mL/min). The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various contributing factors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see Adverse Reactions (6.2)].

Concentration-Adverse Reaction Relationships

There is a relationship between increasing morphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see Dosage and Administration (2.1, 2.2, 2.3)].
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.

In 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 and higher incidence of pseudopregnancies at 20 mg/kg/day (3.2 times the HDO) was reported.

Studies from the literature have also reported changes in hormonal levels in male rats (i.e. testosterone, luteinizing hormone) following treatment with morphine at 10 mg/kg/day or greater (1.6 times the HDO).

Female rats that were administered morphine sulfate intraperitoneally prior to mating exhibited prolonged estrus cycles at 10 mg/kg/day (1.6 times the HDO).

Exposure of adolescent male rats to morphine has been associated with delayed sexual maturation and following mating to untreated females, smaller litters, increased pup mortality, and/or changes in reproductive endocrine status in adult male offspring have been reported (estimated 5 times the plasma levels at the HDO).

14 CLINICAL STUDIES

The analgesic efficacy of EMBEDA has been evaluated in one randomized, double-blind, placebo-controlled clinical trial in osteoarthritics 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 osteoarthritics 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 ≤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, 73.1% 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 V) to the end of study (Visit X+12 Weeks Early Termination) was statistically significantly superior for those treated with EMBEDA compared to the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

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<tr>
<th>Strength</th>
<th>Capsule Content</th>
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<td>20 mg</td>
<td>Grey circle. The body has a single grey band around ¼ of the circumference.</td>
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<td>30 mg</td>
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<td>50 mg</td>
<td>Grey circle. The body has a single grey band around ¼ of the circumference.</td>
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<tr>
<td>60 mg</td>
<td>Grey circle. The body has a single grey band around ¼ of the circumference.</td>
</tr>
<tr>
<td>80 mg</td>
<td>Grey circle. The body has a single grey band around ¼ of the circumference.</td>
</tr>
<tr>
<td>100 mg</td>
<td>Grey circle. The body has a single grey band around ¼ of the circumference.</td>
</tr>
</tbody>
</table>

Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]. 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 and 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 dosage is increased, and that it can occur even at recommended doses [see Warnings and Precautions (5.3)]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see Warnings and Precautions (5.3)]. Instruct patients to take steps to store EMBEDA securely and to dispose of unused EMBEDA by flushing the capsules down the toilet.

Interactions with Alcohol

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.

Inform patients and caregivers that potentially fatal additive effects may occur if EMBEDA is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see Warnings and Precautions (5.5), Drug Interactions (7)].

Sedation

Inform patients that opioids can cause a rare but potentially life-threatening condition resulting from concomitant administration of sedative-hypnotic drugs. Warn patients of the symptoms of sedation and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take sedative drugs [see Drug Interactions (7)].

MAOI Interaction

Inform patients not to take EMBEDA while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking EMBEDA [see Warnings and Precautions (5.7), Drug Interactions (7)].

Adrenal Insufficiency

Inform patients that opioids can cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see Warnings and Precautions (5.8)].

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 [see Dosage and Administration (2.1)].
• Do not crush, chew, or dissolve the pellets contained in the capsules because of a risk of fatal morphine overdose or naltrexone precipitated withdrawal symptoms in opioid-dependent individuals [see Dosage and Administration (2.1, 2.8)].
• Use EMBEDA exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) [see Warnings and Precautions (5.3)].
• Do not discontinue EMBEDA without first discussing the need for a tapering regimen with the prescriber [see Dosage and Administration (2.5)].

Hypotension

Inform patients that EMBEDA may cause orthostatic hypotension and syncope. Instruct patients 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) [see Warnings and Precautions (5.9)].

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 [see Contraindications (4), Adverse Reactions (6.2)].

Pregnancy

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 (5.4), Use in Specific Populations (8.1)].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that EMBEDA can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations (8.1)].

Lactation

Advise patients that breastfeeding is not recommended during treatment with EMBEDA [see Use in Specific Populations (8.2)].

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2)].

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 [see Warnings and Precautions (5.14)].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see Adverse Reactions (6.1)].

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.
EMBEDA® (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.

• Taking EMBEDA with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

• 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

• problems urinating

• 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. Not recommended during treatment with EMBEDA. It 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 and could lead to death.

When taking EMBEDA:

• Do not change your dose. Take EMBEDA exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.

• 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, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

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


This Medication Guide has been approved by the U.S. Food and Drug Administration
Revised: December 2016; LAB-0643-2.0
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:

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

    Figure 1

  - 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 2

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

    Figure 3

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

    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
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