

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: ADDICTION, ABUSE, AND MISUSE; 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

See full prescribing information for complete boxed warning.

- EMBEDA exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1)
- 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. (5.2)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow EMBEDA capsules whole to avoid exposure to a potentially fatal dose of morphine. (5.3)
- Accidental ingestion of EMBEDA, especially by children, can result in fatal overdose of morphine. (5.3)
- Prolonged use of EMBEDA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.4).
- Instruct patients not to consume alcohol or any products containing alcohol while taking EMBEDA because co-ingestion can result in fatal plasma morphine levels. (5.5)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5, 7)

RECENT MAJOR CHANGES

Dosage and Administration (2.5) 102019
Warnings and Precautions (5.3, 5.13) 102019

INDICATIONS AND USAGE

EMBEDA is a combination opioid agonist/opioid antagonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve EMBEDA for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- EMBEDA is not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- 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)

- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg of morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg of oral oxycodone per day, 8 mg of oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Instruct patients to swallow EMBEDA capsules intact, or to sprinkle the capsule contents on applesauce and immediately swallow without chewing. (2.1)
- Instruct patients not to cut, break, crush, dissolve, or chew the pellets in the capsule to avoid the risk of release and absorption of a potentially fatal dose of morphine, and to avoid release of sequestered naltrexone that could precipitate opioid withdrawal. (2.1, 5.1)
- For opioid-naïve and opioid non-tolerant patients, initiate with 20 mg/0.8 mg capsules (morphine sulfate/naltrexone hydrochloride) orally every 24 hours. (2.2)
- Do not abruptly discontinue EMBEDA in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.5, 5.13)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma 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)

WARNINGS AND PRECAUTIONS

- 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)

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

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue EMBEDA if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with EMBEDA because they may reduce analgesic effect of EMBEDA or precipitate withdrawal symptoms. (5.13, 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: 10/2019

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FULL PRESCRIBING INFORMATION

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Addiction, Abuse, and Misuse

EMBEDA[®] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing EMBEDA, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions* (5.1)].

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 REMS for these products [see *Warnings and Precautions* (5.2)]. 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

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of EMBEDA. Monitor for respiratory depression, especially during initiation of EMBEDA or following a dose increase. Instruct patients to swallow EMBEDA capsules whole, or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing, or dissolving the pellets in EMBEDA can cause rapid release and absorption of a potentially fatal dose of morphine [see *Warnings and Precautions* (5.3)].

Accidental Ingestion

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of EMBEDA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions* (5.4)].

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking EMBEDA. The co-ingestion of alcohol with EMBEDA may result in increased plasma level and a potentially fatal overdose of morphine [see *Warnings and Precautions* (5.5)].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions* (5.5), *Drug Interactions* (7)].

- Reserve concomitant prescribing of EMBEDA and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

1 INDICATIONS AND USAGE

EMBEDA is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations [see *Warnings and Precautions (5.1)*], reserve EMBEDA for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- EMBEDA is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

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

EMBEDA 100 mg/4 mg capsules, a single dose greater than 60 mg/2.4 mg, or a total daily dose greater than 120 mg/5 mg, are only for use in patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid-tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg of oral oxycodone per day, 8 mg of oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5)*].
- Initiate the dosing regimen for each patient individually; taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.1)*].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with EMBEDA and adjust the dosage accordingly [see *Warnings and Precautions (5.3)*].

Instruct patients to swallow EMBEDA capsules whole [see *Patient Counseling Information (17)*]. Crushing, chewing, or dissolving EMBEDA capsules will result in uncontrolled delivery of morphine and can lead to overdose or death [see *Warnings and Precautions (5.1)*].

Instruct patients who are unable to swallow EMBEDA to sprinkle the capsule contents on applesauce and immediately swallow without chewing [see *Dosage and Administration (2.6)*].

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

2.2 Initial Dosage

Use of EMBEDA as the First Opioid Analgesic (opioid naive patients)

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

Use of EMBEDA in Patients who are not Opioid Tolerant (opioid-non-tolerant patients)

The starting dose for patients who are not opioid tolerant is EMBEDA 20 mg/0.8 mg orally every 24 hours.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression [see *Warnings and Precautions (5.3)*].

Conversion from Other Opioids to EMBEDA

Discontinue all other around-the-clock opioid drugs when EMBEDA therapy is initiated.

There are no established conversion ratios from other opioids to EMBEDA defined by clinical trials. Initiate dosing using EMBEDA 30 mg orally every 24 hours.

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 are approximations. In general, begin with half of the estimated daily morphine requirement as the initial dose, managing inadequate analgesia by supplementation with immediate-release morphine.

Conversion from Methadone to EMBEDA

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

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

2.3 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 1/3 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 Safe Reduction or Discontinuation of EMBEDA

Do not abruptly discontinue EMBEDA in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking, there are a variety of factors that should be considered, including the dose of EMBEDA the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and

realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on EMBEDA who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic [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.

	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
Extended- Release 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.

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 (5.11)]*
- 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. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing EMBEDA, and monitor all patients receiving EMBEDA for the development of these behaviors 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 detect abuse or diversion 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 (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 that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- 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.opioidanalgesicrem.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 exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of EMBEDA, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression especially during the first 24-72 hours of initiating therapy with and following dosage increases of EMBEDA.

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

Accidental ingestion of even one dose of EMBEDA, especially by children, can result in respiratory depression and death due to an overdose of morphine.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper [see *Dosage and Administration (2.5)*].

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of EMBEDA during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations (8.1)*, *Patient Counseling Information (17)*].

5.5 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of EMBEDA with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [*see Drug Interactions (7)*].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when EMBEDA is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [*see Drug Interactions (7)*, *Patient Counseling Information (17)*].

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on EMBEDA therapy. The co-ingestion of alcohol with EMBEDA may result in increased plasma levels and a potentially fatal overdose of morphine [*see Clinical Pharmacology (12.3)*].

5.6 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of EMBEDA in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with chronic pulmonary disease: EMBEDA-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of EMBEDA [*see Warnings and Precautions (5.3)*].

Elderly, cachectic, or debilitated patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [*see Warnings and Precautions (5.3)*].

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 (5.3, 5.5)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.7 Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, including respiratory depression, coma, and confusion. EMBEDA should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

5.8 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.9 Severe Hypotension

EMBEDA may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is 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)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage 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.

5.10 Use 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

Do not abruptly discontinue EMBEDA in a patient physically dependent on opioids. When discontinuing EMBEDA in a physically dependent patient, gradually taper the dosage. Rapid tapering of morphine and naltrexone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [see *Dosage and Administration* (2.5), *Drug Abuse and Dependence* (9.3)].

Additionally, 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 analgesic, including EMBEDA. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

Consuming EMBEDA capsules that have been altered by crushing, chewing, or dissolving the pellets can release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals. Symptoms of withdrawal usually appear within five minutes of ingestion of naltrexone, can last for up to 48 hours, and can include mental status changes, restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Significant fluid losses from vomiting and diarrhea can require intravenous (IV) fluid administration.

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:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions with Benzodiazepine or Other CNS Depressants *[see Warnings and Precautions (5.5)]*
- Interaction with Monoamine Oxidase Inhibitors *[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 with EMBEDA therapy were constipation, nausea, and somnolence. The most common adverse reactions leading to study discontinuation were nausea, constipation (sometimes severe), vomiting, fatigue, dizziness, pruritus, and somnolence.

Short-Term Randomized Study

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

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

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

Long-Term Open-Label Safety Study

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

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

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

Adverse Reactions Observed in the Phase 2/3 Studies

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

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

Less common ($<1\%$):

Eye disorders: vision blurred, orthostatic hypotension

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

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

Hepatobiliary disorders: cholecystitis

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased

Musculoskeletal and connective tissue disorders: myalgia, muscular weakness

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

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

Renal and urinary disorders: urinary retention, dysuria

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic and mediastinal disorders: dyspnea, rhinorrhea

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

Vascular disorders: hypotension, flushing

6.2 Postmarketing Experience

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.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

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

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in EMBEDA.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see *Clinical Pharmacology* (12.2)].

7 DRUG INTERACTIONS

Table 3 includes clinically significant drug interactions with EMBEDA.

Table 3: Clinically Significant Drug Interactions with EMBEDA

Alcohol	
<i>Clinical Impact:</i>	Concomitant use of alcohol with EMBEDA can result in an increase of morphine plasma levels and potentially fatal overdose of morphine.
<i>Intervention:</i>	Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on EMBEDA therapy [see <i>Warnings and Precautions (5.5)</i> , <i>Clinical Pharmacology (12.3)</i>].
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	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 <i>Dosage and Administration (2.4)</i> and <i>Warnings and Precautions (5.5)</i>].
<i>Examples:</i>	Benzodiazepines, and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue EMBEDA if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.7)</i>].
<i>Intervention:</i>	Do not use EMBEDA in patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
<i>Clinical Impact:</i>	May reduce the analgesic effect of EMBEDA and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
<i>Clinical Impact:</i>	Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	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	
<i>Clinical Impact:</i>	The concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Monitor patients for respiratory depression that may be greater than otherwise expected and decrease the dosage of EMBEDA and/or cimetidine as necessary.
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when EMBEDA is used

	concomitantly with anticholinergic drugs.
P-Glycoprotein (PGP) Inhibitors	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy can cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.4)]. There are no available data with EMBEDA in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Published studies with morphine use during pregnancy have not reported a clear association with morphine and major birth defects [see *Human Data*]. In published animal reproduction studies, morphine administered subcutaneously during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) at 5 and 16 times the human daily dose of 60 mg based on body surface area (HDD) in hamsters and mice, respectively, lower fetal body weight and increased incidence of abortion at 0.4 times the HDD in the rabbit, growth retardation at 6 times the HDD in the rat, and axial skeletal fusion and cryptorchidism at 16 times the HDD in the mouse. Administration of morphine sulfate to pregnant rats during organogenesis and through lactation resulted in cyanosis, hypothermia, decreased brain weights, pup mortality, decreased pup body weights, and adverse effects on reproductive tissues at 3-4 times the HDD; and long-term neurochemical changes in the brain of offspring which correlate with altered behavioral responses that persist through adulthood at exposures comparable to and less than the HDD [see *Animal Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see *Warnings and Precautions* (5.4)].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. EMBEDA is not recommended for use in pregnant women during or immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including EMBEDA, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

The results from a population-based prospective cohort, including 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any time during pregnancy, indicate no increased risk for congenital malformations. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design.

Animal Data

Formal reproductive and developmental toxicology studies for morphine have not been conducted. Exposure margins for the following published study reports are based on human daily dose of 60 mg morphine using a body surface area comparison (HDD). Neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of morphine sulfate (35-322 mg/kg) on Gestation Day 8 to pregnant hamsters (4.7 to 43.5 times the HDD). A no adverse effect level was not defined in

this study and the findings cannot be clearly attributed to maternal toxicity. Neural tube defects (exencephaly), axial skeletal fusions, and cryptorchidism were reported following a single subcutaneous (SC) injection of morphine sulfate to pregnant mice (100-500 mg/kg) on Gestation Day 8 or 9 at 200 mg/kg or greater (16 times the HDD) and fetal resorption at 400 mg/kg or higher (32 times the HDD). No adverse effects were noted following 100 mg/kg morphine in this model (8 times the HDD). In one study, following continuous subcutaneous infusion of doses greater than or equal to 2.72 mg/kg to mice (0.2 times the HDD), exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted. The effects were reduced with increasing daily dose; possibly due to rapid induction of tolerance under these infusion conditions. The clinical significance of this report is not clear.

Decreased fetal weights were observed in pregnant rats treated with 20 mg/kg/day morphine sulfate (3.2 times the HDD) from Gestation Day 7 to 9. There was no evidence of malformations despite maternal toxicity (10% mortality). In a second rat study, decreased fetal weight and increased incidences of growth retardation were noted at 35 mg/kg/day (5.7 times the HDD) and there was a reduced number of fetuses at 70 mg/kg/day (11.4 times the HDD) when pregnant rats were treated with 10, 35, or 70 mg/kg/day morphine sulfate via continuous infusion from Gestation Day 5 to 20. There was no evidence of fetal malformations or maternal toxicity.

An increased incidence of abortion was noted in a study in which pregnant rabbits were treated with 2.5 (0.8 times the HDD) to 10 mg/kg morphine sulfate via subcutaneous injection from Gestation Day 6 to 10. In a second study, decreased fetal body weights were reported following treatment of pregnant rabbits with increasing doses of morphine (10-50 mg/kg/day) during the pre-mating period and 50 mg/kg/day (16 times the HDD) throughout the gestation period. No overt malformations were reported in either publication; although only limited endpoints were evaluated.

In published studies in rats, exposure to morphine during gestation and/or lactation periods is associated with: decreased pup viability at 12.5 mg/kg/day or greater (2 times the HDD); decreased pup body weights at 15 mg/kg/day or greater (2.4 times the HDD); decreased litter size, decreased absolute brain and cerebellar weights, cyanosis, and hypothermia at 20 mg/kg/day (3.2 times the HDD); alteration of behavioral responses (play, social-interaction) at 1 mg/kg/day or greater (0.2 times the HDD); alteration of maternal behaviors (e.g., decreased nursing and pup retrievals) in 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 brain and neuronal 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 for 5 days with escalating doses of 120 to 240 mg/kg/day morphine sulfate (9.7 to 19.5 times the HDD) or when female mice 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 3.6 times the HDD).

8.2 Lactation

Risk Summary

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, including excess sedation and 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 effected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats [*See Nonclinical Toxicology (13.1)*].

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 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)*].

Elderly patients (aged 65 years or older) may have increased sensitivity to EMBEDA. In general, use caution when selecting a dosage for an elderly patient, usually 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. Titrate 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 Schedule II controlled substance.

9.2 Abuse

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.

Drug addiction 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, 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 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 "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(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. 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 also measured in two studies (Study 2, Study 3) on a bipolar 100-point VAS where 0 represents the strongest negative response (e.g., 'definitely would not'), 50 represents a neutral response, and 100 represents the strongest positive response (e.g., 'definitely would'). The pharmacokinetics of morphine sulfate and naltrexone hydrochloride were also determined in these abuse potential studies. When EMBEDA was crushed and administered by the oral and intranasal routes, morphine and naltrexone were absorbed with similar median time-to-peak concentration (T_{max}) values of 1 hour following oral administration and approximately 36 minutes following intranasal administration.

Oral Studies:

Study 1 compared EMBEDA to IR morphine sulfate. In this study 32 subjects received four treatments: 120 mg/4.8 mg as intact EMBEDA capsules, 120 mg/4.8 mg as crushed EMBEDA in solution, 120 mg IR morphine in solution, and placebo. When EMBEDA

was crushed and taken orally, the geometric mean (\pm SD) values for naltrexone C_{\max} and AUC_{inf} were 1073 ± 721 pg/mL and 3649 ± 1868 pg·hr/mL, respectively. The oral administration of crushed EMBEDA was associated with statistically significantly lower mean and median Drug Liking and Drug High scores compared with crushed IR morphine (as summarized in Table 4).

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

Study 2 compared EMBEDA to ER morphine sulfate. In this study 36 subjects were randomized to receive three treatments in solution: 120 mg/4.8 mg as crushed EMBEDA capsules, 120 mg crushed ER morphine, and placebo. When EMBEDA was crushed and taken orally, the geometric mean (\pm SD) values for naltrexone C_{\max} , AUC_{0-2h} , and AUC_{inf} were 824 ± 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 85% of subjects had some reduction in Drug Liking with crushed EMBEDA compared to administration of crushed ER morphine sulfate, while approximately 15% had no reduction in Drug Liking. Similarly, 100% of subjects showed some reduction in Drug High with crushed EMBEDA compared to crushed ER morphine. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to crushed ER morphine was observed in 76% and 52% of subjects, respectively (summarized in Figure 1). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 79% and 64% of subjects, respectively.

Table 4. Summary of Abuse Potential Maximal Responses (E_{\max}) with Oral Administration of Crushed EMBEDA Compared to Crushed IR Morphine Sulfate (Study 1) or Crushed ER Morphine (Study 2)

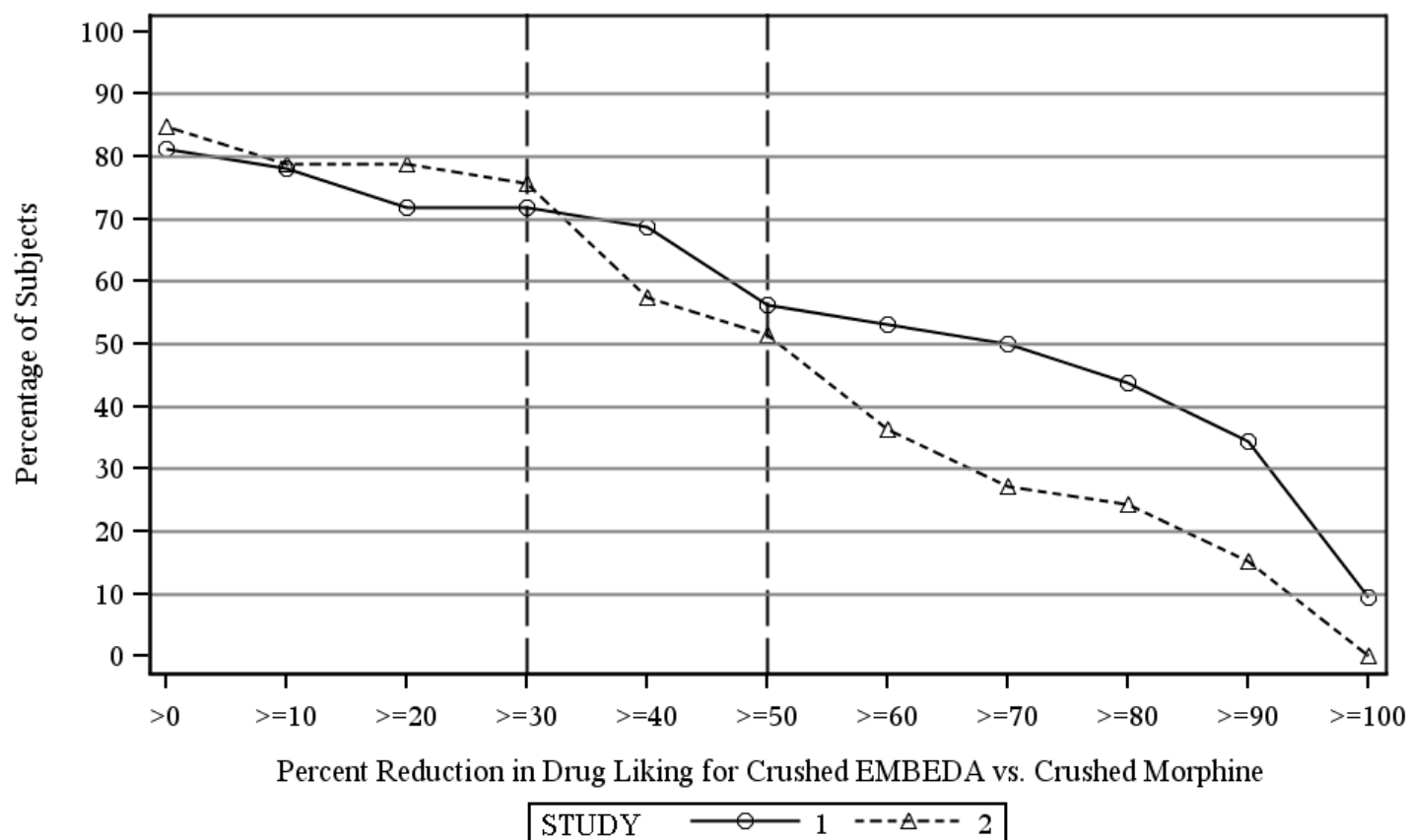
VAS Scale (100 point)		E_{\max}	
		Crushed EMBEDA (120 mg/4.8 mg)	Crushed Morphine (120 mg)
Study 1			Immediate Release
Drug Liking*	Mean (SE)	68.1 (3.1)	89.5 (2.2)
	Median (range)	62 (50-100)	93 (57-100)
Drug High**	Mean (SE)	54.7 (6.1)	90.2 (2.1)
	Median (range)	64 (0-100)	97 (61-100)
Study 2			Extended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

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

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

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

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



Intranasal Study:

Study 3 compared intranasal administration of crushed EMBEDA to crushed ER morphine sulfate. In this study, 33 subjects were randomized to receive three treatments: 30 mg/1.2 mg as crushed EMBEDA, 30 mg crushed ER morphine, and crushed placebo. When EMBEDA was crushed and taken intranasally, the geometric mean (\pm SD) values for naltrexone C_{\max} , AUC_{0-2h} , and AUC_{inf} were 1441 ± 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 70% of subjects showed some reduction in Drug High with crushed EMBEDA compared to crushed ER morphine and approximately 30% of subjects had no reduction in Drug High. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to crushed ER morphine was observed in 63% and 59% of subjects, respectively (summarized in Figure 2). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 59% and 37% of subjects, respectively.

Table 5. Summary of Abuse Potential Maximal Responses (E_{\max}) with Intranasal Administration of Crushed EMBEDA Compared to Crushed ER Morphine Sulfate (Study 3)

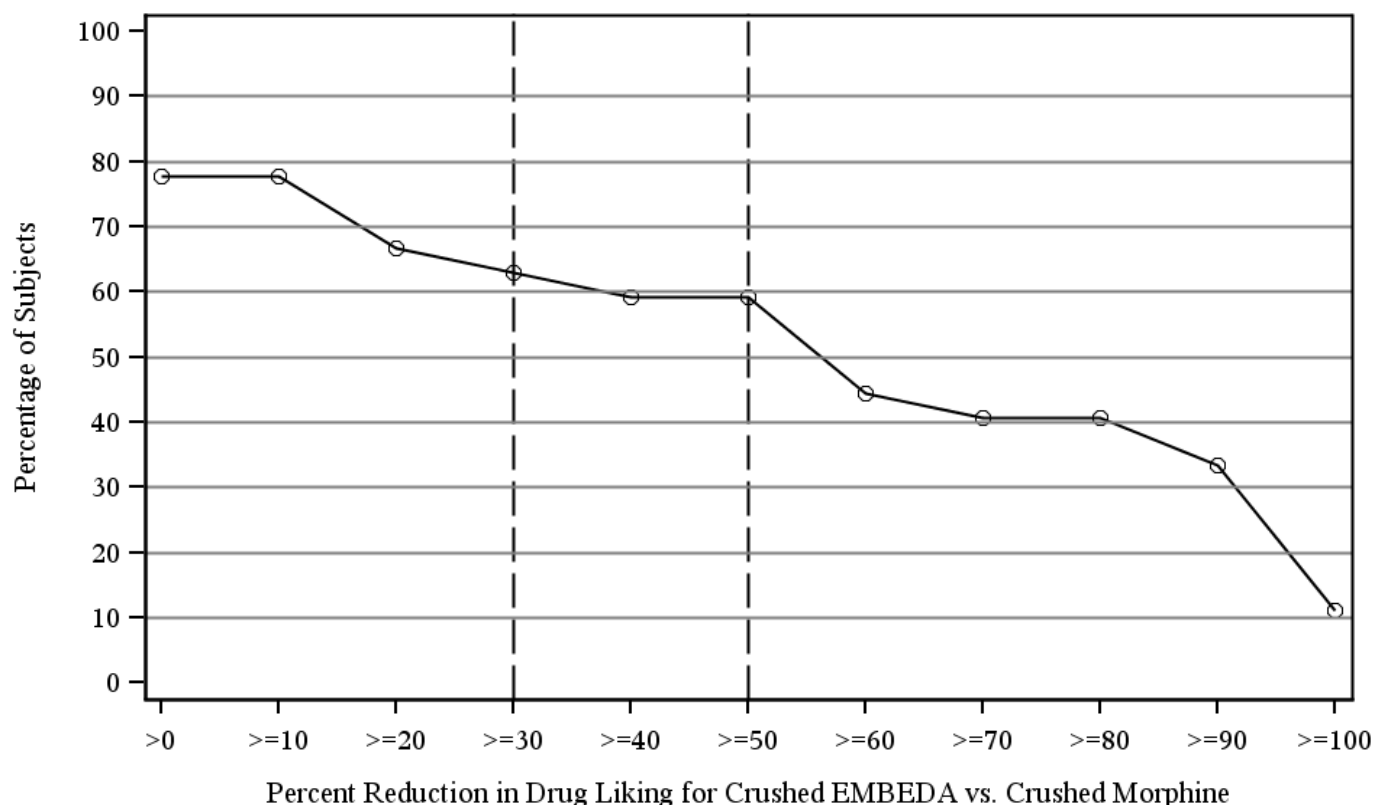
VAS Scale (100 point)		E_{\max}	
		Crushed EMBEDA (30 mg/1.2 mg)	Crushed ER Morphine (30 mg)
Drug Liking*	Mean (SE)	69.0 (3.5)	88.4 (3.2)
	Median (range)	66 (50-100)	100 (51-100)
Drug High**	Mean (SE)	48.6 (7.8)	84.4 (3.8)
	Median (range)	51 (-39-100)	100 (42-100)
Take Drug Again*	Mean (SE)	59.1 (5.4)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

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

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

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

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



Simulated IV Study:

Study 4, a randomized double-blind, placebo-controlled, three-way cross-over trial in 28 non-dependent recreational opioid users, was performed using 30 mg of intravenous (IV) morphine sulfate alone and 30 mg of IV morphine sulfate in combination with 1.2 mg of IV naltrexone to simulate parenteral use of crushed EMBEDA. These doses were based on the assumption of the complete release of both morphine sulfate and naltrexone hydrochloride upon crushing EMBEDA. Intravenous administration of the combination of morphine sulfate and naltrexone hydrochloride was associated with statistically significantly lower mean and median Drug Liking and Drug High scores (median scores 34 and 23, respectively) compared with morphine alone (median scores 86 and 89, respectively). Three of the 26 subjects who completed the study had no reduction in Drug Liking and all the subjects showed some reduction in Drug High. Intravenous injection of crushed EMBEDA may result in serious injury and death due to a morphine overdose and may precipitate a severe withdrawal syndrome in opioid-dependent patients.

Summary

The in vitro and pharmacokinetic data demonstrate that crushing EMBEDA pellets results in the simultaneous release and rapid absorption of morphine sulfate and naltrexone hydrochloride. These data along with results from the oral and intranasal human abuse potential studies indicate that EMBEDA has properties that are expected to reduce abuse via the oral and intranasal route. However, abuse of EMBEDA by these routes is still possible.

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

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

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

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue EMBEDA in a patient physically dependent on opioids. Rapid tapering of EMBEDA in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing EMBEDA, gradually taper the dosage using a patient-specific plan that considers the following: the dose of EMBEDA the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper [see *Dosage and Administration (2.5), Warnings and Precautions (5.13)*].

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 (8.1)*].

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

11 DESCRIPTION

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

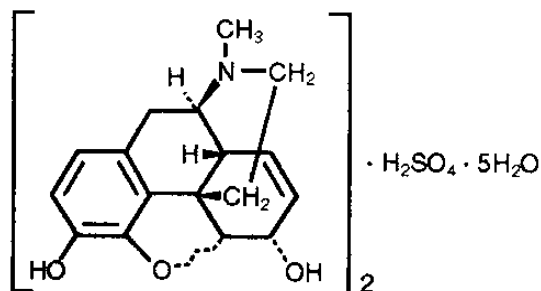
Each EMBEDA extended-release capsule contains the following inactive ingredients common to all strengths: talc, ammonio methacrylate copolymer, sugar spheres, ethylcellulose, sodium chloride, polyethylene glycol, hydroxypropyl cellulose, dibutyl sebacate, methacrylic acid copolymer, diethyl phthalate,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

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

Morphine Sulfate

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

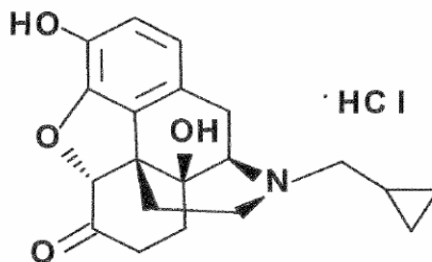
Morphine sulfate is an odorless, white, crystalline powder with a bitter taste. It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol:water partition coefficient of morphine is 1.42 at physiologic pH and the pK_b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



Naltrexone Hydrochloride

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

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



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Morphine Sulfate

Morphine 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 compounds with 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 contractions 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 low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors 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 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, 2.3)*].

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 (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.

Naltrexone

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

Compared to 2.4 mg naltrexone oral solution, which produced mean (SD) naltrexone plasma levels of 689 (\pm 429 pg/mL) and mean (SD) 6 β -naltrexol plasma levels of 3920 (\pm 1350 pg/mL), administration of intact 60 mg EMBEDA produced no naltrexone plasma levels and mean (SD) 6 β -naltrexol plasma levels of 16.7 (\pm 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.

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 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)].

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-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.

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).

Hepatic Impairment

Morphine pharmacokinetics are altered in patient with alcoholic cirrhosis. 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

Morphine pharmacokinetics are altered in patients with renal failure. The AUC is increased and clearance is decreased and the metabolites, M3G and M6G, may 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 Studies

Alcohol

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

Long-term 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 and higher incidence of pseudopregnancies at 20 mg/kg/day (3.2 times the HDD) were 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 HDD).

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

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 HDD).

14 CLINICAL STUDIES

The analgesic efficacy of EMBEDA has been evaluated in one randomized, double-blind, placebo-controlled clinical trial in osteoarthritis patients with moderate to severe pain (Study ALO-KNT-301). This study, with a randomized withdrawal design, was conducted in subjects with moderate to severe pain from osteoarthritis of the hip or knee over a 12-week treatment period. Subjects started open-label treatment with EMBEDA and titrated to effect. Once their pain was controlled (Brief Pain Inventory [BPI] Average 24-hour Pain Intensity ≤ 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
Extended- Release Capsule Description For all strengths, the darker-toned cap has “EMBEDA” printed in grey ink and a single grey band around $\frac{3}{4}$ of the circumference.	Two-toned, yellow opaque hard gelatin capsule. The lighter-toned body has “20” reverse-printed in a grey circle.	Two-toned, blue-violet opaque hard gelatin capsule. The lighter-toned body has “30” reverse-printed in a grey circle.	Two-toned, blue opaque hard gelatin capsule. The lighter-toned body has “50” reverse-printed in a grey circle.	Two-toned, pink opaque hard gelatin capsule. The lighter-toned body has “60” reverse-printed in a grey circle.	Two-toned, light peach opaque elongated hard gelatin capsule. The lighter-toned body has “80” reverse-printed in a grey circle.	Two-toned, green opaque hard gelatin capsule. The lighter-toned body has “100” reverse-printed in a grey circle.
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) [see USP Controlled Room Temperature]. Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store EMBEDA securely and dispose of properly [see *Patient Counseling Information* (17)].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use)

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store EMBEDA securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home [see *Warnings and Precautions* (5.3, 5.13), *Drug Abuse and Dependence* (9.2)]. Inform patients that leaving EMBEDA unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused EMBEDA should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

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)].

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.

Interactions with Benzodiazepines and Other CNS Depressants

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)].

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications [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 could 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 due to a risk of fatal morphine overdose or naltrexone precipitated withdrawal symptoms in opioid-dependent individuals [see *Dosage and Administration* (2.1, 2.6)].
- Use EMBEDA exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) [see *Warnings and Precautions* (5.3)].

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue EMBEDA without first discussing a tapering plan with the prescriber [see *Dosage and Administration* (2.5)].

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) [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)].

**This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>**

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)*].

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



LAB-0599-7.1

Medication Guide

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 else your EMBEDA. They could die from taking it. Selling or giving away EMBEDA is against the law.
- Store EMBEDA securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not take EMBEDA if you have:

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

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

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of EMBEDA during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** 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.**
- Dispose of expired, unwanted, or unused EMBEDA by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

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

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

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: October 2019; LAB-0643-2.1

Instructions For Use
EMBEDA® (im-bed-a)
(morphine sulfate and naltrexone hydrochloride) extended-release Capsules, CII

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

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

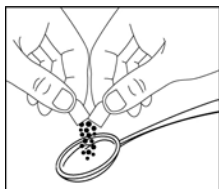


Figure 1

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



Figure 2

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



Figure 3

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



Figure 4

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

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

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

Manufactured for: Pfizer Inc, New York, NY 10017

by: Actavis Elizabeth LLC, 200 Elmora Avenue, Elizabeth, NJ 07207

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