

Cost of Antibiotic Resistance Hits Private Payers

VITALS

Major Finding: The overall cost of antimicrobial resistance is rising, but because patients now are younger and living longer, the burden has shifted from Medicare to private insurance.

Data Source: Two studies assessing hospital database data and one Internet survey.

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BY MIRIAM E. TUCKER

BETHESDA, MD. — The overall cost burden of antimicrobial resistance—as high as \$38 billion in one 2009 hospital estimate—has shifted sharply from Medicare to private payers over the last decade.

Medicare still pays the majority of the costs for excess length of stay, increased use of more expensive drugs,

and poorer health attributable to treatment-resistant infections. However, the rise in infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), which largely affects younger, healthier individuals, has meant that the overall cost per patient has declined but more is being borne by private HMOs and PPOs, Susan D. Foster, Ph.D., said at the 2010 Conference on Antimicrobial Resistance sponsored

by the National Foundation for Infectious Diseases.

“There’s been a major shift in who’s actually paying. I don’t think the insurance companies are quite aware of this,” said Dr. Foster, professor of international health at Boston University and director of public policy and education for the Alliance for the Prudent Use of Antibiotics at Tufts University, Boston.

EMBEDA™ (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules for oral use - ©

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

The following is a brief summary only. For complete product information, please see Full Prescribing Information, including Medication Guide, on www.EMBEDA.com.

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

EMBEDA contains pellets of an extended-release oral formulation of morphine sulfate, an opioid receptor agonist, surrounding an inner core of naltrexone hydrochloride, an opioid receptor antagonist indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

EMBEDA is NOT intended for use as a prn analgesic.

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

Patients should not consume alcoholic beverages while on EMBEDA therapy. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on EMBEDA therapy. The co-ingestion of alcohol with EMBEDA may result in an increase of plasma levels and potentially fatal overdose of morphine. EMBEDA is to be swallowed whole or the contents of the capsules sprinkled on apple sauce. The pellets in the capsules are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of morphine.

Crushing, chewing, or dissolving EMBEDA will also result in the release of naltrexone which may precipitate withdrawal in opioid-tolerant individuals.

INDICATIONS AND USAGE: EMBEDA is an extended-release oral formulation of morphine sulfate and naltrexone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. EMBEDA is NOT intended for use as a prn analgesic. EMBEDA is not indicated for acute/postoperative pain or if the pain is mild or not expected to persist for an extended period of time. EMBEDA is only indicated for postoperative use if the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. **CONTRAINDICATIONS:** EMBEDA is contraindicated in patients with a known hypersensitivity to morphine, morphine salts, naltrexone, or in any situation where opioids are contraindicated. **Impaired Pulmonary Function:** EMBEDA is contraindicated in patients with significant respiratory depression in unmonitored settings or the absence of resuscitative equipment. EMBEDA is contraindicated in patients with acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment [see Warnings and Precautions]. **Paralytic Ileus:** EMBEDA is contraindicated in any patient who has or is suspected of having paralytic ileus. **WARNINGS AND PRECAUTIONS: EMBEDA is to be swallowed whole or the contents of the capsules sprinkled on apple sauce. The pellets in the capsules are not to be crushed, dissolved, or chewed. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals. In opioid-tolerant individuals, the absorption of naltrexone may increase the risk of precipitating withdrawal. EMBEDA 100 mg/4 mg is for use in opioid-tolerant patients only. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.**

Misuse, Abuse, and Diversion of Opioids: EMBEDA contains morphine, an opioid agonist, and is a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing EMBEDA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Abuse of EMBEDA by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death [see Drug Abuse and Dependence]. Concerns about abuse and addiction should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse of this product.

Interactions with Alcohol and Drugs of Abuse: EMBEDA may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result. Patients should not consume alcoholic beverages, prescription or non-prescription medications containing alcohol while on EMBEDA therapy. The co-ingestion of alcohol with EMBEDA can result in an increase of morphine plasma levels and potentially fatal overdose of morphine [see Clinical Pharmacology]. **Impaired Respiration:** Respiratory depression is the chief hazard of all morphine preparations such as EMBEDA. Respiratory depression occurs more frequently and is more dangerous in elderly and debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction (when even moderate therapeutic doses may significantly decrease pulmonary ventilation). EMBEDA should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose. **Head Injury and Increased Intracranial Pressure:** The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. EMBEDA can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in pressure in patients with head injuries. EMBEDA should only be administered under such circumstances when considered essential and then with extreme care. **Hypotensive Effect:** EMBEDA may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has already been compromised by a reduced blood volume or a concurrent administration of drugs such as phenothiazines or general anesthetics [see Drug Interactions]. EMBEDA may produce orthostatic hypotension and syncope in ambulatory patients. EMBEDA should be administered with caution to patients in circulatory shock, as vasodilation

produced by the drug may further reduce cardiac output and blood pressure. **Interactions with other CNS Depressants:** EMBEDA should be used with caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result [see Drug Interactions]. **Gastrointestinal Effects:** EMBEDA should not be given to patients with gastrointestinal obstruction, particularly paralytic ileus, as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored. As with other solid morphine formulations diarrhea may reduce morphine absorption. The administration of morphine may obscure the diagnosis or clinical course in patients with acute abdominal condition. **Cordotomy:** Patients taking EMBEDA who are scheduled for cordotomy or other interruption of pain transmission pathways should have EMBEDA ceased 24 hours prior to the procedure and the pain controlled by parenteral short-acting opioids. In addition, the post-procedure titration of analgesics for such patients should be individualized to avoid either oversedation or withdrawal syndromes. **Use in Pancreatic/Biliary Tract Disease:** EMBEDA may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase level. **Tolerance and Physical Dependence:** 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). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are common during chronic opioid therapy. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other 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. EMBEDA should not be abruptly discontinued [see Dosage and Administration]. **Special Risk Groups:** EMBEDA should be administered with caution, and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; patients with Addison's disease; myxedema; hypothyroidism; prostatic hypertrophy or urethral stricture. Caution should also be exercised in the administration of EMBEDA to patients with CNS depression, toxic psychosis, acute alcoholism, and delirium tremens. All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings. **Driving and Operating Machinery:** EMBEDA may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of EMBEDA with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics, and alcohol [see Drug Interactions]. **Anaphylaxis:** Although extremely rare, cases of anaphylaxis have been reported with the use of a similar extended release morphine formulation. **Accidentally Precipitated Withdrawal:** Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with EMBEDA. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of EMBEDA and/or may precipitate withdrawal symptoms in these patients. Consuming EMBEDA that have been tampered by crushing, chewing, or dissolving the extended-release formulation can release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals. Symptoms of withdrawal usually appear within five minutes of ingestion of naltrexone and can last for up to 48 hours. Mental status changes can include confusion, somnolence, and visual hallucinations. Significant fluid losses from vomiting and diarrhea can require intravenous fluid administration. Patients should be closely monitored and therapy with non-opioid medications tailored to meet individual requirements. **Laboratory Tests:** Naltrexone does not interfere with thin-layer, gas-liquid, and high pressure liquid chromatographic methods which may be used for the separation and detection of morphine, methadone, or quinidine in the urine. Naltrexone may or may not interfere with enzymatic methods for the detection of opioids depending on the specificity of the test. Please consult the test manufacturer for specific details. **ADVERSE REACTIONS:** Serious adverse reactions that may be associated with EMBEDA therapy in clinical use include: respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock [see Overdosage, Warnings and Precautions]. The common adverse events seen on initiation of therapy with EMBEDA are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent of these include drowsiness, dizziness, constipation, and nausea. **Clinical Studies Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. There were 1251 subjects exposed to at least one dose of EMBEDA in the clinical program. During late phase clinical development, 618 subjects received EMBEDA in two randomized, controlled, double-blind studies in subjects with osteoarthritis of the hip or knee. An additional 465 subjects received EMBEDA in an open-label, year-long safety study of subjects with chronic, non-cancer pain, 208 subjects for at least six months and 124 for 12 months. The remaining 168 subjects were exposed to a single dose of EMBEDA in early PK/PD studies. **Short-Term (12-Week) Randomized Study – Adverse reactions observed in at least 2% of subjects treated with EMBEDA:** 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, subjects were randomized to either active treatment with EMBEDA or were tapered off EMBEDA using a double-dummy design and placed on placebo. The Maintenance Period was 12 weeks. The most common adverse reactions leading to study discontinuation were nausea, constipation, vomiting, fatigue, dizziness, pruritus, and somnolence. Adverse reactions, defined as treatment-related adverse events assessed by the investigators, reported by $\geq 2.0\%$ of subjects in either the titration or maintenance phase of the 12-week study are presented in Table 1.

Table 1: Adverse Events Reported by $\geq 2.0\%$ of Subjects in 12-Week Efficacy Study – Safety Population

System Organ Class Preferred Term	Titration		Maintenance	
	EMBEDA (N=547) n (%)	n (%)	EMBEDA (N=171) n (%)	Placebo (N=173) n (%)
Subjects With At Least One TEAE	313 (57.2%)		56 (32.7%)	45 (26.0%)
Gastrointestinal disorders	260 (47.5%)		41 (24.0%)	28 (16.2%)
Abdominal pain upper	6 (1.1%)		4 (2.3%)	3 (1.7%)
Constipation	165 (30.2%)		12 (7.0%)	7 (4.0%)
Diarrhoea	6 (1.1%)		12 (7.0%)	12 (6.9%)
Dry mouth	31 (5.7%)		3 (1.8%)	2 (1.2%)
Nausea	106 (19.4%)		19 (11.1%)	11 (6.4%)

Dr. Foster analyzed data from three studies. In an unpublished study, she and her associates reviewed Massachusetts hospital discharge data from 2000 to 2007 to look for ICD-9 "VO9" codes, which are specific for drug-resistant infections. Although these codes are difficult to use and therefore represent a study limitation, they do allow for analysis of trends over time, she explained.

Overall, the number of hospital discharges reporting antibiotic resistance in Massachusetts increased from 3,861 in 2000 to 11,218 in 2007. The inflation-adjusted total cost more than doubled over

the 7 years, from \$135 to \$285 million. However, the length of stay (LOS) per patient for drug-resistant infections dropped by 4.5 days, and the cost per patient fell by nearly \$10,000.

In contrast, the length of stay for drug-susceptible infections didn't change during the study period (just under 5 days), while the cost per patient with susceptible infections rose only slightly.

The drop in LOS and cost per patient with drug-resistant infections is largely explained by the dramatic shift in patient age, particularly among 19- to 64-year-olds: In 2000, that age group accounted

for 30% of drug-resistant infection discharges, whereas in 2007 the proportion had risen to 45.5%. At the same time, the 65- to 80-year-old group dropped from 38% to 25%. While the proportion of infections due to drug-resistant organisms rose in all age groups, the greatest rise was among working-age adults, Dr. Foster noted.

Not surprisingly, then, was the concurrent payer shift: Medicare's proportion of the cost dropped from 73% in 2000 to 58% in 2007, while Medicaid's rose from 6% to 15%. The proportion paid by "other," including private insur-

ance, rose from 20.5% to 28%, she said.

There were also declines in inpatient mortality due to drug-resistant infections (from 11% to 5%) and in discharge of patients to nursing homes (32% to 28%), with a concomitant increase in patients returning home from the hospital (33% to 48%).

The second study, conducted by Dr. Rebecca Roberts and her associates for the Chicago Antimicrobial Resistance Project, analyzed discharge data at Cook County Hospital for a random sample of 1,391 high-risk (more than five ICD-9 codes, excluding trauma, burn, or obstetric care) adult patients, of whom

13.5% (188) had an antibiotic-resistant infection (ARI). Societal costs for the study year 2000 were estimated at \$10.7-\$15 million, or \$13.35 million in 2008 dollars (Clin. Infect. Dis. 2009;49:1175-84).

In that study, LOS was three times longer for the patients with ARIs (24 vs. 8 days) and mortality 6 times higher (18% vs. 3%). Total inpatient costs were \$58,029, compared with \$13,210 for non-ARI patients. Even the daily cost was \$517 greater for the ARI group, she noted.

The most common type of ARI was MRSA (43%), followed by vancomycin-resistant enterococci (VRE, 31%), *Escherichia coli*/*Klebsiella* species (16%), and multiple infections (6%). By cost, however, VRE accounted for the greatest proportion (36%), followed by MRSA (34%), and multiple infections (16%).

After publication of the study, Dr. Foster collaborated with Dr. Roberts in extrapolating the Chicago data to the entire United States: In 2000, there were 900,000 admissions with the same criteria the study used. Applying the costs found in that study gives \$16.6-\$26 billion in additional health care costs (the range reflects different inflation adjustments). Updating the figure to 2009 costs using the Consumer Price Index gives an estimated \$21-\$34 billion, while using medical inflation rates boosts the figures to as high as \$24-\$38 billion.

The third study, also unpublished work by Dr. Foster and her associates, was an Internet-based survey of more than 300 respondents recruited from MRSA chat rooms, listservs, and Google Adwords. Acknowledging the limitations of such surveys—particularly the bias toward younger, healthier Internet users with strong opinions—she described "some heart-rending responses," including one from parents who felt they had to send their children away to prevent transmission.

Respondents reported a mean out-of-pocket expenditure of \$2,251, including copays for office visits, prescription drugs, and hospital stays. Nearly 70% reported having private insurance (HMO or PPO), and 14% said they were uninsured, which approximately reflects the national average, Dr. Foster said.

"Individuals and households affected by drug resistance bear a large uncompensated burden in terms of out-of-pocket expenses and lost wages," she concluded.

Table 1 (contd)

System Organ Class Preferred Term	Titration		Maintenance	
	EMBEDA (N=547) n (%)	n (%)	EMBEDA (N=171) n (%)	Placebo (N=173) n (%)
Vomiting	46 (8.4%)		7 (4.1%)	2 (1.2%)
General disorders and administration site conditions				
Fatigue	39 (7.1%)		9 (5.3%)	10 (5.8%)
Nervous system disorders				
Fatigue	16 (2.9%)		1 (0.6%)	2 (1.2%)
Dizziness	135 (24.7%)		12 (7.0%)	11 (6.4%)
Headache	42 (7.7%)		2 (1.2%)	2 (1.2%)
Somnolence	22 (4.0%)		4 (2.3%)	2 (1.2%)
Psychiatric disorders				
Somnolence	76 (13.9%)		2 (1.2%)	5 (2.9%)
Insomnia	34 (6.2%)		10 (5.8%)	9 (5.2%)
Skin and subcutaneous tissue disorders				
Pruritus	7 (1.3%)		5 (2.9%)	4 (2.3%)
Vascular disorders				
Flushing	46 (8.4%)		7 (4.1%)	7 (4.0%)
Flushing	34 (6.2%)		0	1 (0.6%)
Flushing	4 (0.7%)		5 (2.9%)	2 (1.2%)
Flushing	0		4 (2.3%)	1 (0.6%)

¹Adverse reactions are classified by System Organ Class and Preferred Term as defined by the Medical Dictionary of Regulatory Affairs (MedDRA) v9.1. If a subject had more than one AE that codes to the same Preferred Term, the subject was counted only once for that Preferred Term. **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 events. Adverse reactions, defined as treatment-related adverse events assessed by the investigators, reported by $\geq 2.0\%$ of subjects are presented immediately below. **Adverse Reactions Reported by $\geq 2.0\%$ of Subjects in Long-Term Safety Study – Safety Population (N=465):** Any Related AE 288 (61.9%); Gastrointestinal disorders 219 (47.1%); Constipation 145 (31.2%); Diarrhoea 10 (2.2%); Dry mouth 17 (3.7%); Nausea 103 (22.2%); Vomiting 37 (8.0%); General disorders and administration site conditions 51 (11.0%); Fatigue 19 (4.1%); Nervous system disorders 99 (21.3%); Dizziness 19 (4.1%); Headache 32 (6.9%); Somnolence 34 (7.3%); Psychiatric disorders 42 (9.0%); Anxiety 10 (2.2%); Insomnia 13 (2.8%); Skin and subcutaneous tissue disorders 52 (11.2%); Hyperhidrosis 16 (3.4%); Pruritus 26 (5.6%). Adverse reactions are classified by System Organ Class and Preferred Term as defined by the Medical Dictionary of Regulatory Affairs (MedDRA) v9.1. If a subject had more than one AE that codes to the same Preferred Term, the subject was counted only once for that Preferred Term. **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. **Adverse Reactions Observed in the Phase 2/3 Studies: Most common ($\geq 10\%$):** Gastrointestinal disorders: constipation, nausea; Nervous system disorders: somnolence. **Common ($\geq 1\%$ to $<10\%$):** Gastrointestinal disorders: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence, stomach discomfort, vomiting; General disorders and administration site conditions: chills, edema peripheral, fatigue, irritability; Metabolism and nutrition disorders: anorexia, decreased appetite; Musculoskeletal and connective tissue disorders: arthralgia, muscle spasms; Nervous system disorders: dizziness, headache, lethargy, sedation, tremor; Psychiatric disorders: anxiety, depression, insomnia, restlessness; Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus; Vascular disorders: hot flush. **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, paraesthesia, 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, rhinorrhoea; Skin and subcutaneous tissue disorders: rash, piloerection, cold sweat, night sweats; Vascular disorders: hypotension, flushing. **USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects:** Pregnancy Category C: Teratogenic effects of morphine have been reported in the animal literature. High parental doses during the second trimester were teratogenic in neurological, soft and skeletal tissue. The abnormalities included encephalopathy and axial skeletal fusions. These doses were often maternally toxic and were 0.3 to 3-fold the maximum recommended human dose (MRHD) on a mg/m² basis. The relative contribution of morphine-induced maternal hypoxia and malnutrition, each of which can be teratogenic, has not been clearly defined. Treatment of male rats with approximately 3-fold the MRHD for 10 days prior to mating decreased litter size and viability. **Nonteratogenic Effects:** Morphine given subcutaneously, at non-maternally toxic doses, to rats during the third trimester with approximately 0.15-fold the MRHD caused reversible reductions in brain and spinal cord volume, and testes size and body weight in the offspring, and decreased fertility in female offspring. The offspring of rats and hamsters treated orally or intraperitoneally throughout pregnancy with 0.04- to 0.3-fold the MRHD of morphine have demonstrated delayed growth, motor and sexual maturation, and decreased male fertility. Chronic morphine exposure of fetal animals resulted in mild withdrawal, altered reflex and motor skill development, and altered responsiveness to morphine that persisted into adulthood. There are no well-controlled studies of chronic *in utero* exposure to morphine sulfate in human subjects. However, uncontrolled retrospective studies of human neonates chronically exposed to other opioids *in utero*, demonstrated reduced brain volume which normalized over the first month of life. Infants born to opioid-abusing mothers are more often small for gestational age, have a decreased ventilatory response to CO₂, and increased risk of sudden infant death syndrome. There are no adequate and well-controlled studies of naltrexone in pregnant women. EMBEDA should only be used

during pregnancy if the need for strong opioid analgesia justifies the potential risk to the fetus. **Labor and Delivery:** EMBEDA is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor 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 dilatation which tends to shorten labor. Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate. **Nursing Mothers:** Morphine is excreted in the maternal milk, and the milk to plasma morphine AUC ratio is about 2.5:1. The amount of morphine received by the infant depends on the maternal plasma concentration, amount of milk ingested by the infant, and the extent of first pass metabolism. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Because of the potential for adverse reactions in nursing infants from EMBEDA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and efficacy of EMBEDA in individuals less than 18 years of age have not been established. **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. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, 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. **Neonatal Withdrawal Syndrome:** Chronic maternal use of opiates or opioids during pregnancy coexists with the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NWS). Manifestations of NWS include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The onset, duration, and severity of the disorder differ based on such factors as the addictive drug used, time and amount of mother's last dose, and rate of elimination of the drug from the newborn. Approaches to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paregoric or phenobarbital. **Race:** Pharmacokinetic differences due to race may exist. Chinese subjects given intravenous morphine in one study had a higher clearance when compared to Caucasian subjects (1852 \pm 116 mL/min versus 1495 \pm 80 mL/min). **Hepatic Failure:** The pharmacokinetics of morphine was found to be significantly altered in individuals with alcoholic cirrhosis. The clearance was found to decrease with a corresponding increase in half-life. The morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) to morphine plasma AUC ratios also decreased in these patients indicating a decrease in metabolic activity. **Renal Insufficiency:** The pharmacokinetics of morphine is altered in renal failure patients. AUC is increased and clearance is decreased. The metabolites, M3G and M6G, accumulate several fold in renal failure patients compared with healthy subjects. Adequate studies of naltrexone in patients with severe hepatic or renal impairment have not been conducted. **Breakthrough Pain/Adverse Experiences:** Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication. **Mental and/or Physical Ability:** Patients should be advised that EMBEDA may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on EMBEDA or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected. [See Warnings and Precautions]. **Avoidance of Alcohol or Other CNS Depressants:** Patients should be advised that EMBEDA should not be taken with alcohol, prescription or non-prescription medications containing alcohol, or other CNS depressants (sleeping medication, tranquilizers) except by the orders of the prescribing healthcare provider because dangerous additive effects may occur resulting in serious injury or death [See Warnings and Precautions]. **Pregnancy:** Women of childbearing potential who become or are planning to become pregnant, should consult their prescribing healthcare provider prior to initiating or continuing therapy with EMBEDA [See Use in Specific Populations]. **Cessation of Therapy:** Patients should be advised that if they have been receiving treatment with EMBEDA for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the EMBEDA dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their prescribing healthcare provider should provide a dose schedule to accomplish a gradual discontinuation of the medication. **Drug of Abuse:** Patients should be advised that EMBEDA is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed [See Warnings and Precautions]. **Constipation:** Patients should be advised that severe constipation could occur as a result of taking EMBEDA and appropriate laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy. **Storage/Destruction of Unused EMBEDA:** Patients should be instructed to keep EMBEDA in a secure place out of the reach of children. When EMBEDA is no longer needed, the unused capsules should be destroyed by flushing down the toilet.

FDA-Approved Patient Labeling

[See separate leaflet.]

Manufactured for: King Pharmaceuticals, Inc., 501 Fifth Street, Bristol, TN 37620

(Telephone: 1-800-776-3637)

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