

H1N1 Vaccine Being Tested in Asthma Patients

BY MICHELE G. SULLIVAN

A new phase II trial will test the safety and efficacy of the pandemic influenza A(H1N1) vaccine in patients with mild, moderate, and severe asthma.

Although the vaccine has already been approved as safe and effective in the general population, additional studies are necessary to confirm its effect on those

with asthma—especially those who take glucocorticoid medications, Dr. Anthony Fauci said in a statement.

“People with severe asthma often take high doses of glucocorticoids that can suppress their immune system, placing them at greater risk for infection and possibly serious disease caused by 2009 H1N1 influenza virus,” said Dr. Fauci, director of the National Institute of Allergy and Infectious Disease (NIAID). “We need to de-

termine the optimal dose of 2009 H1N1 influenza vaccine that can be safely administered to this at-risk population and whether one or two doses are needed.”

The study, sponsored by NIAID and the National Heart, Lung, and Blood Institute, plans to enroll 350-400 healthy subjects aged 12 years and older with mild, moderate, or severe asthma. Participants will be stratified into two groups: those with mild to moderate versus those with

severe asthma. All participants will be randomly assigned to receive either high-dose (30 mcg) or low-dose (15 mcg) H1N1 vaccine. In addition to studying adverse events and immune response, researchers will look for any effect the vaccine may have on asthma indicators.

The study will last 34 weeks, and will be conducted in Georgia, Missouri, Ohio, North Carolina, Pennsylvania, Virginia, and Wisconsin. ■

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 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. 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 ≥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 ≥2.0% of Subjects in 12-Week Efficacy Study – Safety Population

System Organ Class Preferred Term	Titration		Maintenance	
	EMBEDA (N=547) n (%) ¹	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%)