Melanoma Incidence Expected to Rise This Year

BY DOUG BRUNK

SAN DIEGO — Data on the estimated incidence of melanoma in the United States in 2010 from the National Cancer Institute's Surveillance, Epidemiology and End Results program will not be available until later this year, but Dr. Darrell S. Rigel does not expect the news to be good.

"Melanoma rates are rising significantly in the United States and in other parts of the world," he said at a melanoma update sponsored by the Scripps Clinic. "Whatever criteria you use, it's clear that we're seeing more melanomas than we've seen in the past, and we'll probably continue to do so in the next 5-10 years."

According to the most recent SEER data, in 2009 there were 68,720 newly diagnosed cases of invasive melanoma and 53,120 cases of in situ melanoma. Dr. Rigel and his associates at the New York University Interdisciplinary Melanoma Cooperative Group estimate that the projected lifetime risk of invasive melanoma was 1:58 in 2009, up from 1:65 in 2004.

"Should that rate of increase continue, the risk will be about 1:50 by the year 2015," said Dr. Rigel, professor of dermatology and dermatologic surgery at New York University Medical Center. "We've been pretty close on these projections over the last few years. One in 50 is a lot. That's 2% of the population."

Factor in the incidence of in situ melanoma, and the risk of any American getting any kind of melanoma jumps to 1:30, which would be 121,840 total cases in 2009.

"It's a significant problem," he said.

Nine years ago, researchers who analyzed the melanoma incidence rates in

Important Safety Information (contd)

- EMBEDA® is contraindicated in patients with a known hypersensitivity to morphine, morphine salts, naltrexone, or in any situation where opioids are contraindicated
- 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
- EMBEDA® is contraindicated in any patient who has or is suspected of having paralytic ileus
- 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
- 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
- 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
- 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. 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
- 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
- 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
- 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
- EMBEDA® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis
- 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
- EMBEDA® should be administered with caution and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; 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

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including boxed warning, on the following pages.

the United States from 1960-1997 forecasted a subsequent growing incidence of melanoma. They concluded that the increase in melanoma incidence is real—"not due to improved diagnosis," Dr. Rigel said—and predicted that the incidence would continue to rise for the next decade or more (J. Natl. Cancer Inst. 2001;93:67-83).

Results from studies published in the past decade suggest that the incidence of melanoma is also rising in other parts of the world. In Finland, for example, the incidence of melanoma increased from 1.5 cases to 12.8 cases per 100,000 men between 1953 and 2003, and from 1.8 cases to 10.4 cases per 100,000 women during the same time period (Int. J. Cancer 2006;119:380-4).

In central Greece, the incidence increased from 1.4 cases to 5.2 cases per 100,000 people between 1988 and 1998 (Int. J. Tissue React. 2005;27:173-9). Melanomas were most frequently located on the head and neck, extremities, and trunk. In Columbia, the incidence of melanoma increased from 2.7 cases to 13 cases per 100,000 people between 2003 and 2005 (Rev. Salud Pública 2007;9:595-601).

Dr. Rigel emphasized that results from the best available studies in the medical literature suggest that the rising incidence of melanoma cannot be explained by increased surveillance, awareness, or by changing histologic criteria. However, while the number of melanoma deaths continues to rise, 5-year survival rates are improving—from 86% between 1985 and 1989 to 92% between 1995 and 2002 (Cancer J. Clin. 2007;57:43-66).

"That seems incongruous," Dr. Rigel said. "The only way that can be happening mathematically is that the incidence has to be rising even faster. That's a compelling reason to explain why the rising incidence is real. According to the World Health Organization, melanoma is rising faster than any other cancer worldwide, on a percentage basis."

He went on to note that the current incidence of melanoma is probably underreported because data from SEER are collected primarily from hospitals.

Dr. Rigel disclosed that he receives grants and advising and consulting fees from a number of pharmaceutical companies, including Neutrogena, Johnson & Johnson, Procter & Gamble, and Beiersdorf. ■

- 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
- 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 has been tampered with 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
- **Care should be taken to use low initial doses of EMBEDA® in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications**
- EMBEDA® should not be abruptly discontinued
- 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
- 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 part of opioid analgesia. The most frequent of these include drowsiness, dizziness, constipation, and nausea
- Additional common adverse events reported during clinical studies include constipation, nausea, and somnolence
- EMBEDA® should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol because of the risk of respiratory depression, hypotension, and profound sedation or coma. When such combined therapy is contemplated, the initial dose of one or both agents should be reduced by at least 50%
- EMBEDA® may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression
- Monoamine oxidase inhibitors (MAOIs) have been reported to potentiate the effects of morphine anxiety, confusion, and significant depression of respiration or coma. EMBEDA® should not be used in patients taking MAOIs or within 14 days of stopping such treatment
- There is an isolated report of confusion and severe respiratory depression when a hemodialysis patient was concurrently administered morphine and cimetidine
- Morphine can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism
- Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus

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

Please see Brief Summary of full Prescribing Information, including boxed warning, on the following pages.

References: 1. Embeda (package insert). Bristol, TN: King Pharmaceuticals®, Inc; 2009. **2.** Data on file. King Pharmaceuticals®, Inc.

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