Facts About BELBUCA™ (buprenorphine) Buccal Film

Indication	BELBUCA™ is a recent FDA-approved medication for the treatment of chronic pain severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate.
Administration	BELBUCA™ provides buprenorphine in an optimally-designed delivery system known as BEMA® (BioErodible MucoAdhesive) technology, which efficiently and conveniently delivers buprenorphine across the buccal mucosa (inner lining of the cheek). BELBUCA is the first and only oral pain medicine combining the proven efficacy and established safety of buprenorphine – a widely used opioid analgesic for severe chronic pain as well as opioid dependence – with the BEMA® delivery system.
Dosage	BELBUCA™ offers dosing flexibility. There will be seven dosages available in Q1 2016, allowing for treatment ranges from 75 µg to 900 µg.
Pivotal Data	The approval of BELBUCA™ is based on two pivotal, phase 3, double-blind randomized, placebo-controlled, enriched-enrollment studies in patients with moderate to severe chronic lower back pain. A total of 971 randomized patients completed both trials, including pain sufferers who either had received opioid therapy (study EN3409-307) or were opioid-naïve at the start of the study (study EN3409-308). *Efficacy:* Overall, average pain scores increased more in the placebo arm versus BELBUCA™ at week 12 from baseline, and the difference between the two groups was statistically significant: • (EN3409-307) mean score change: 1.92, placebo versus 0.88, BELBUCA™; p<0.00001 • (EN3409-308) mean score change: 1.59, placebo versus 0.94, BELBUCA™; p=0.0012 A statistically significant percentage of patients on BELBUCA™ versus placebo experienced pain reductions of greater than 30 percent compared to placebo (EN3409-307: 64.2 percent versus 30.6 percent; p<0.0001; EN3409-308: 62.7 percent versus 46.9 percent; p=0.0012). *Safety:* BELBUCA™ has a well-understood tolerability profile. The most commonly reported adverse events in the double-blind treatment phase (occurring in 3 percent or more of patients) were: • EN3409-307: Nausea (7 percent), vomiting (5 percent), constipation (3 percent), drug withdrawal syndrome (3 percent), and urinary tract infection (3 percent) with BELBUCA™; Drug withdrawal syndrome (10 percent), nausea (7 percent), upper respiratory tract infection (4 percent), headache (3 percent), diarrhea (3 percent), and anxiety (3 percent) with placebo • EN3409-308: Nausea (10 percent), constipation (4 percent), and vomiting (4 percent) with BELBUCA™; Nausea (7 percent), constipation (6 percent), upper respiratory tract infection (4 percent), headache (3 percent), and diarrhea (3 percent) with placebo
Controlled Substance Designation	BELBUCA™ is a mu-opioid receptor partial agonist. It is a Schedule III controlled substance, defined as having lower abuse potential than Schedule II drugs, a category that includes most opioid analgesics.
Development	Buprenorphine Buccal Film was developed and is being commercialized through a worldwide license and development agreement between Endo Pharmaceuticals and BioDelivery Sciences International, Inc., which developed the BEMA delivery system.

INDICATION

BELBUCA™ (buprenorphine) buccal film 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 long-acting opioid formulations, reserve BELBUCA™ for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- BELBUCA™ is not indicated as an as-needed (prn) analgesic.

IMPORTANT SAFETY INFORMATION about BELBUCA™

WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Addiction, Abuse, and Misuse

BELBUCA™ 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 BELBUCA™, and monitor patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of BELBUCA™. Monitor for respiratory depression, especially during initiation of BELBUCA™ or following a dose increase. Misuse or abuse of BELBUCA™ by chewing, swallowing, snorting, or injecting buprenorphine extracted from the buccal film will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death.

Accidental Exposure

Accidental exposure to even one dose of BELBUCA™, especially by children, can result in a fatal overdose of buprenorphine.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of BELBUCA™ 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.

CONTRAINDICATIONS

BELBUCA™ is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Hypersensitivity (eg, anaphylaxis) to buprenorphine

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

- BELBUCA™ contains buprenorphine, a Schedule III controlled substance. As an opioid, BELBUCA™ exposes users to the risks of addiction, abuse, and misuse.
- Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing BELBUCA™, and monitor all patients receiving BELBUCA™ for the development of these behaviors or 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 (eg, 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 BELBUCA™, but use in such patients necessitates intensive counseling about the risks and proper use of BELBUCA™, along with intensive monitoring for signs of addiction, abuse, or misuse.
- Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BELBUCA™ and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.
- Abuse or misuse of BELBUCA™ by swallowing may cause choking, overdose, and death.
- Opioid agonists such as BELBUCA™ are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Strategies to reduce the risk include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug.
- Contact a local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.
- BELBUCA™ should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Education and training programs that meet FDA requirements are offered by accredited CME/CE providers, and are available to prescribers of extended-release opioids at no or nominal cost. A list of these programs can be found at www.er-la-opioidREMS.com or by calling 1-800-503-0784. An FDA-approved patient counseling document for healthcare providers containing important safety information regarding the safe use, storage, and disposal of extended-release opioids can also be obtained or downloaded at www.er-la-opioidREMS.com.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of buprenorphine, even when used as recommended. Respiratory depression, from opioid use, 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.
- While serious, life-threatening or fatal respiratory depression can occur at any time during the use of BELBUCA™, the risk is greatest during initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with BELBUCA™ and following dose increases.
- To reduce the risk of respiratory depression, proper dosing and titration of BELBUCA™ are essential. Overestimating the dose of BELBUCA™ when converting patients from another opioid product may result in fatal overdose with the first dose.
- Accidental exposure to BELBUCA™, especially in children, can result in respiratory depression and death due to an overdose of buprenorphine.

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of BELBUCA™ during pregnancy can result in withdrawal signs 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. 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.
- Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, failure to gain weight; and there have been reports of convulsions, apnea, respiratory depression, and bradycardia. 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.

Risks due to Interactions with Central Nervous System Depressants

- Hypotension, profound sedation, coma, or respiratory depression may result if BELBUCA™ is used concomitantly with alcohol or other CNS depressants (eg, sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).
- When considering the use of BELBUCA™ in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin therapy with BELBUCA™ is made, start with a lower dosage of BELBUCA™, monitor patients for signs of sedation, respiratory depression, and hypotension, and consider using a lower dosage of the concomitant CNS depressant.

Risk of Life-Threatening Respiratory Depression in Elderly, Cachectic, and Debilitated Patients

- Monitor elderly, cachectic, or debilitated patients closely, particularly when initiating and titrating BELBUCA™ and when BELBUCA™ is given concomitantly with other drugs that depress respiration. Life-threatening respiratory depression is more likely to occur in these patients, as they may have altered pharmacokinetics or altered clearance compared with younger, healthier patients.

Risk of Apnea in Patients with Chronic Pulmonary Disease

- BELBUCA™-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of BELBUCA™. Therefore, closely monitor these patients, especially when initiating and titrating BELBUCA™. Alternatively, consider the use of alternative non-opioid analgesics in these patients.

QTc Prolongation

- BELBUCA™ has been observed to prolong the QTc interval in some subjects participating in clinical trials. Consider these observations in clinical decisions when prescribing BELBUCA™ to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of BELBUCA™ in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III

antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval.

Severe Hypotension

- BELBUCA™ may cause severe hypotension including orthostatic hypotension and syncope, in ambulatory patients. There is an 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 (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dose of BELBUCA™. Avoid the use of BELBUCA™ in patients with circulatory shock, because BELBUCA™ may cause vasodilation that can further reduce cardiac output and blood pressure.

Risks of Use in Patients with Head Injury or Increased Intracranial Pressure

- In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), BELBUCA™ may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with BELBUCA™.
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of BELBUCA™ in patients with impaired consciousness or coma.

Hepatotoxicity

- Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving sublingual formulations of buprenorphine for the treatment of opioid dependence, both in clinical trials and in post-marketing adverse events reports. For patients at increased risk of hepatoxicity (e.g., patients with a history of excessive alcohol intake, intravenous drug abuse or liver disease), obtain baseline liver enzyme levels and monitor periodically during treatment with BELBUCA™.

Risk of Overdose in Patients With Moderate or Severe Hepatic Impairment

- In a pharmacokinetic study of subjects dosed with buprenorphine sublingual tablets, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment but not in subjects with mild hepatic impairment. For patients with severe hepatic impairment, a dose adjustment is recommended, and patients with moderate or severe hepatic impairment should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Anaphylactic/Allergic Reactions

- Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported.

Risk of Use in Patients with Gastrointestinal Conditions

- BELBUCA™ may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders

- Buprenorphine may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during BELBUCA™ therapy.

Risks of Use in Cancer Patients with Oral Mucositis

- Cancer patients with oral mucositis may absorb buprenorphine more rapidly than intended and are likely to experience transiently higher plasma levels of the opioid. A dose reduction is recommended in these patients. Monitor carefully for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Risks of Driving and Operating Machinery

- BELBUCA™ may impair the mental and 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 side effects of BELBUCA™ and know how they will react to the medication.

ADVERSE REACTIONS

- The most common adverse reactions (≥5%) reported by patients treated with BELBUCA™ in the clinical trials were nausea, constipation, headache, vomiting, fatigue, dizziness, somnolence, diarrhea, dry mouth, and upper respiratory tract infection.