



PLEASE JOIN US FOR A LIVE PRESENTATION

Addressing Unmet Needs of Chronic Pain Patients Taking Opioid Therapy

WEDNESDAY, SEPTEMBER 8, 2021

BRERA Ballroom
3355 S Las Vegas Boulevard
Las Vegas, NV 89109

PRESENTED BY

Ketan Patel, MD
National Spine & Pain Centers

PROGRAM AGENDA

12:30 PM – 1:30 PM PT Presentation & Lunch

HOSTED BY

Pierson Van Raalte
201-953-0547

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Pursuant to the PhRMA Code on Interactions with Healthcare Professionals, attendance at this promotional program is restricted to healthcare professionals. Accordingly, spouses and other guests who are not healthcare professionals may not attend this event.

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Ketan Patel, MD

Haymarket, VA



Dr. Patel is an executive physician at National Spine & Pain Centers. He currently serves as the medical director of the Haymarket, VA location and the interim medical director for the Aldie, VA location. In 2012, he completed his fellowship training in interventional pain management at the University of California, Los Angeles (UCLA), where he received advanced training in non-surgical techniques by one of the field's preeminent experts.

Prior to his fellowship, Dr. Patel completed his residency training in anesthesiology at the renowned Johns Hopkins Hospital, during which time he authored content for a leading pain management textbook.

Patel is board-certified in anesthesiology and pain management. He has received numerous awards and distinctions throughout his academic and professional career, including the multi-year reciprocity of Northern Virginia Top Doctors. He maintains active memberships in the American Society of Interventional Pain Physicians (ASIPP) and the North American Neuromodulation Society (NANS). He serves as the co-founder and vice-president of the DMV Pain Society.

Dr. Patel is a highly respected clinician and educator with the unique ability to teach complex concepts in a palatable and tangible way.

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 (e.g., 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; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS

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 regularly for these behaviors and conditions.

Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the FDA has required a 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

- 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 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 poses a significant risk of overdose and death.

Accidental Exposure

Accidental exposure to even one dose of BELBUCA, especially in 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. 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.

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. 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.

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; and hypersensitivity (e.g., 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. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BELBUCA. Addiction can occur at recommended dosages and if the drug is misused or abused.
- 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 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 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.
- Consider prescribing naloxone for the emergency treatment of opioid overdose.
- Abuse or misuse of BELBUCA by swallowing may cause choking, overdose, and death.
- Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing BELBUCA. 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.

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 FDA has required a 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. To obtain further information on the REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com
- Healthcare providers are strongly encouraged to complete a REMS-compliant education program; to discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients or caregivers; to emphasize to patients and caregivers the importance of reading the Medication Guide; and to consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

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.
- 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 dosage increase. Monitor patients closely for respiratory depression when initiating therapy with BELBUCA and following dosage 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. Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.
- 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.
- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with BELBUCA. Also consider prescribing

naloxone based on the patient's risk factors for overdose or if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone.

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of BELBUCA 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.

Risks due to Interactions with Benzodiazepines or Other Central Nervous System Depressants

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of BELBUCA 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.

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. Follow patients closely for signs and symptoms of respiratory depression and sedation.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose.

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

- The use of BELBUCA in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.
- BELBUCA-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with 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 BELBUCA.
- Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared with younger, healthier patients.
- Monitor such patients closely, particularly when initiating and titrating BELBUCA and when BELBUCA is given concomitantly with other drugs that depress respiration.

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.

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 (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of BELBUCA. In patients with circulatory shock, BELBUCA may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of BELBUCA in patients with circulatory shock.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

- In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), BELBUCA 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 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 hepatotoxicity (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.

Withdrawal

- Do not abruptly discontinue BELBUCA in a patient physically dependent on opioids. When discontinuing BELBUCA in a physically dependent patient, gradually taper the dosage. Rapid tapering of buprenorphine in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain.
- Additionally, the use of BELBUCA, a partial agonist opioid analgesic, in patients who are receiving a full opioid agonist analgesic may reduce the analgesic effect and/or precipitate withdrawal symptoms. Avoid concomitant use of BELBUCA with a full opioid agonist analgesic.

Risk of Use in Patients with Gastrointestinal Conditions

- BELBUCA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.
- 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

- The buprenorphine in BELBUCA 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 higher plasma levels of the opioid. For patients with known or suspected mucositis, a dose reduction is recommended. Monitor these patients 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, and somnolence.

Please see [full Prescribing Information](#), including **Boxed Warning**, and [Medication Guide](#) for BELBUCA.

To report SUSPECTED ADVERSE REACTIONS, contact BioDelivery Sciences International, Inc. at 1-800-469-0261 or FDA at 1-800-FDA-1088 or www.fda.gov/safety/medwatch.

Intended for healthcare professionals of the United States of America only.

INDICATION

SYMPROIC[®] (naldemedine) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Patients with known or suspected gastrointestinal (GI) obstruction and patients at increased risk of recurrent obstruction, due to the potential for GI perforation.
- Patients with a history of a hypersensitivity reaction to naldemedine. Reactions have included bronchospasm and rash.

WARNINGS AND PRECAUTIONS

Cases of GI perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue if this symptom develops.

Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting have occurred in patients treated with SYMPROIC[®].

Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Take into account the overall risk-benefit profile when using SYMPROIC[®] in such patients. Monitor for symptoms of opioid withdrawal in such patients.

DRUG INTERACTIONS

Avoid use with strong CYP3A inducers (e.g., rifampin) because they may reduce the efficacy of SYMPROIC[®].

Use with moderate (e.g., fluconazole) and strong (e.g., itraconazole) CYP3A inhibitors and P-glycoprotein inhibitors (e.g., cyclosporine) may increase SYMPROIC[®] concentrations. Monitor for potential adverse reactions.

Avoid use of SYMPROIC[®] with another opioid antagonist due to the potential for additive effect and increased risk of opioid withdrawal.

USE IN SPECIFIC POPULATIONS

Naldemedine crosses the placenta and may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. SYMPROIC[®] should be used during pregnancy only if the potential benefit justifies the potential risk. Because of the potential for serious adverse reactions, including opioid withdrawal in breastfed infants, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

Avoid use in patients with severe hepatic impairment. No dose adjustment of SYMPROIC[®] is required in patients with mild or moderate hepatic impairment.

ADVERSE REACTIONS

The most common adverse reactions with SYMPROIC[®] compared to placebo in two pooled 12-week studies were: abdominal pain (8% vs 2%), diarrhea (7% vs 2%), nausea (4% vs 2%), and gastroenteritis (2% vs 1%).

The incidence of adverse reactions of opioid withdrawal in two pooled 12-week studies was 1% (8/542) for SYMPROIC[®] and 1% (3/546) for placebo. In a 52-week study, the incidence was 3% (20/621) for SYMPROIC[®] and 1% (9/619) for placebo.

Please see [Full Prescribing Information](#) and [Medication Guide](#) for SYMPROIC[®].

To report SUSPECTED ADVERSE REACTIONS, contact BioDelivery Sciences International, Inc. at 1-800-469-0261 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Intended for healthcare professionals of the United States of America only.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

BELBUCA® (buprenorphine buccal film), CIII
Initial U.S. Approval: 1981

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- BELBUCA exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1, 10)
- 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 on proper administration of BELBUCA to reduce the risk. (5.3)
- Accidental exposure to BELBUCA, especially in children, can result in fatal overdose of buprenorphine. (5.3)
- Prolonged use of BELBUCA 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)
- 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 (2.2) 03/2021
Warnings and Precautions (5.1, 5.3, 5.5) 03/2021

-----INDICATIONS AND USAGE-----

BELBUCA buccal film contains buprenorphine, a partial opioid agonist. BELBUCA 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. (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 long-acting opioid formulations, reserve BELBUCA 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)
- BELBUCA is not indicated as an as-needed (prn) analgesic. (1)

-----DOSAGE AND ADMINISTRATION-----

- To be prescribed only by health care providers knowledgeable in use of potent opioids for management of chronic pain. (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)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with BELBUCA. Consider prescribing naloxone based on the patient's risk factors for overdose. (2.2, 5.1, 5.3, 5.5)

- For opioid-naïve patients: Initiate therapy with 75 mcg BELBUCA once daily or every 12 hours, as tolerated, for at least 4 days before increasing dose to 150 mcg every 12 hours. (2.3)
- Conversion from other opioids to BELBUCA: Taper current daily opioid dose to 30 mg oral morphine sulfate equivalents (MSE) or less prior to initiating therapy with BELBUCA. (2.3)
 - For patients taking less than 30 mg oral MSE, initiate therapy with 75 mcg once daily or every 12 hours. (2.3)
 - For patients taking between 30 mg and 89 mg oral MSE, initiate therapy with 150 mcg BELBUCA every 12 hours following analgesic taper. (2.3)
 - For patients taking between 90 mg and 160 mg oral MSE, initiate therapy with 300 mcg BELBUCA every 12 hours following analgesic taper. (2.3)
 - For patients taking greater than 160 mg oral MSE, consider alternate analgesic. (2.3)
- BELBUCA doses of 600 mcg, 750 mcg, and 900 mcg are only for use following titration from lower doses of BELBUCA. (2.3)
- Do not abruptly discontinue BELBUCA in a physically-dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.5)
- Patients with Severe Hepatic Impairment: Reduce the starting and incremental dose by half that of patients with normal liver function. (2.6, 5.11, 8.6)
- Patients with Oral Mucositis: Reduce the starting and incremental dose by half that of patients without mucositis. (2.7)

-----DOSAGE FORMS AND STRENGTHS-----

Buccal film available in 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg dosage strengths. (3)

-----CONTRAINDICATIONS-----

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to buprenorphine (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. (5.7)
- Risk of Prolonged QTc Interval: Avoid in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications. (5.8, 12.2)
- Severe Hypotension: Monitor during dose initiation and titration. Avoid use of BELBUCA in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of BELBUCA in patients with impaired consciousness or coma. (5.10)

-----ADVERSE REACTIONS-----

Most common adverse reactions (>5%) include nausea, constipation, headache, vomiting, dizziness, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioDelivery Sciences International, Inc. at 1-800-469-0261 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Benzodiazepines: May increase buprenorphine-induced respiratory depression. Monitor patients on concurrent therapy closely. (7)
- CYP3A4 Inhibitors/Inducers: Initiating CYP3A4 inhibitors or discontinuing CYP3A4 inducers may result in an increase in buprenorphine plasma concentrations. Closely monitor patients starting CYP3A4 inhibitors or stopping CYP3A4 inducers for respiratory depression. (7)
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue BELBUCA if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with BELBUCA because they may reduce analgesic effect of BELBUCA or precipitate withdrawal symptoms. (7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of buprenorphine. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: May cause fetal harm. (8.1)

- **Lactation:** Not recommended. (8.2)
- **Moderate or Severe Hepatic Impairment:** Monitor for signs and symptoms of toxicity or overdose. (5.11, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2021

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FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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 all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions (5.1)* and *Overdosage (10)*].

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 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 [see *Warnings and Precautions (5.3)*].

Accidental Exposure

Accidental exposure to even one dose of BELBUCA, especially in children, can result in a fatal overdose of buprenorphine [see *Warnings and Precautions (5.3)*].

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 [see *Warnings and Precautions (5.4)*].

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 BELBUCA 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

BELBUCA 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 [*see Warnings and Precautions (5.1)*], reserve BELBUCA 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.
- BELBUCA is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

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

- 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 BELBUCA and adjust the dosage accordingly [*see Warnings and Precautions (5.3)*].

BELBUCA buccal film is for oral buccal use only and is to be applied to the buccal mucosa every 12 hours.

Instruct patients not to use BELBUCA if the pouch seal is broken or the buccal film is cut, damaged, or changed in any way and to avoid applying BELBUCA to areas of the mouth with any open sores or lesions.

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with BELBUCA [*see Warnings and Precautions (5.3), Patient Counseling Information (17)*].

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient [*see Warnings and Precautions (5.1, 5.3, 5.5)*].

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

2.3 Initial Dosing

Use of BELBUCA as the Initial Opioid Analgesic (opioid-naïve patients) or in Patients who are not Opioid Tolerant (opioid-non-tolerant patients)

Initiate treatment in opioid-naïve and opioid-non-tolerant patients with a 75 mcg film once daily or, if tolerated, every 12 hours (see [Table 1](#)) for at least 4 days, then increase dose to 150 mcg every 12 hours. Individual titration to a dose that provides adequate analgesia and minimizes adverse reactions should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days. Doses up to 450 mcg every 12 hours were studied in opioid-naïve patients in the clinical trials [*see Clinical Studies (14)*].

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 BELBUCA

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

There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids. To reduce the risk of opioid withdrawal, taper patients to no more than 30 mg oral morphine sulfate equivalents (MSE) daily before beginning BELBUCA. Following analgesic taper, base the starting dose on the patient's daily opioid dose prior to taper, as described in [Table 1](#). Patients may require additional short-acting analgesics during the taper period and during titration.

BELBUCA may not provide adequate analgesia for patients requiring greater than 160 mg oral MSE per day. Consider the use of an alternate analgesic.

There is inter-patient variability in the relative potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of BELBUCA. It is safer to underestimate a patient's 24-hour oral buprenorphine dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour buprenorphine dosage and manage an adverse reaction due to overdose.

In a BELBUCA clinical trial with an open-label titration period, patients were converted from their prior opioid to BELBUCA using [Table 1](#) as a guide for the initial BELBUCA dose.

Table 1: Initial BELBUCA Dose Based on Prior Opioid Expressed as Oral Morphine Sulfate Equivalents

Prior Daily Dose of Opioid Analgesic Before Taper to 30 mg Oral MSE	Initial BELBUCA Dose
Less than 30 mg oral MSE	BELBUCA 75 mcg once daily or every 12 hours
30 mg to 89 mg oral MSE	BELBUCA 150 mcg every 12 hours
90 mg to 160 mg oral MSE	BELBUCA 300 mcg every 12 hours
Greater than 160 mg oral MSE	Consider alternate analgesic

BELBUCA doses of 600 mcg, 750 mcg, and 900 mcg are only for use following titration from lower doses of BELBUCA. Individual titration should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days.

Conversion from Methadone to BELBUCA

Close monitoring is of particular importance when converting from methadone to other opioid agonists, including BELBUCA. 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.

2.4 Titration and Maintenance of Therapy

Individually titrate BELBUCA to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving BELBUCA to assess the maintenance of pain control and the relative incidence of adverse reactions and monitor 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 dosage adjustment of BELBUCA 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 BELBUCA dose.

The minimum titration interval of BELBUCA is 4 days, based on the pharmacokinetic profile and time to reach steady-state plasma levels [see *Clinical Pharmacology (12.3)*]. Individual titration should proceed in increments of no more than 150 mcg every 12 hours.

The maximum BELBUCA dose is 900 mcg every 12 hours. Do not exceed a dose of BELBUCA 900 mcg every 12 hours due to the potential for QTc interval prolongation [see *Warnings and Precautions (5.8)*, *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.2)*]. If pain is not adequately managed on BELBUCA 900 mcg, consider an alternate analgesic.

If unacceptable opioid-related adverse reactions are observed, adjust the dose to obtain an appropriate balance between the management of pain and opioid-related adverse reactions.

2.5 Safe Reduction or Discontinuation of BELBUCA

Do not abruptly discontinue BELBUCA 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 BELBUCA, there are a variety of factors that should be considered, including the dose of BELBUCA 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 comorbid 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 BELBUCA 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 (5.14)*, *Drug Abuse and Dependence (9.3)*].

2.6 Dosage Modifications in Patients with Severe Hepatic Impairment

In patients with severe hepatic impairment (i.e., Child-Pugh C), reduce the starting dose and reduce the titration dose by half that of patients with normal liver function, from 150 mcg to 75 mcg [see *Warnings and Precautions (5.12)*, *Use in Special Populations (8.6)*, *Clinical Pharmacology (12.3)*].

2.7 Dosage Modifications in Patients with Oral Mucositis

In patients with known or suspected mucositis, reduce the starting dosage and titration incremental dosage by half compared to patients without mucositis [see *Warnings and Precautions (5.17)*, *Clinical Pharmacology (12.3)*].

2.8 Administration of BELBUCA

BELBUCA should not be used if the package seal is broken or the film is cut, damaged, or changed in any way.

First, the patient must use the tongue to wet the inside of the cheek or rinse the mouth with water to wet the area for placement of BELBUCA. BELBUCA is then applied immediately after removal from the individually sealed package. The yellow side of the BELBUCA film is placed against the inside of the cheek. The entire BELBUCA film is held in place with clean, dry fingers for 5 seconds and then left in place on the inside of the cheek until fully dissolved.

BELBUCA adheres to the moist buccal mucosa and will completely dissolve after application, usually within 30 minutes. The film should not be manipulated with the tongue or finger(s) and eating food and drinking liquids should be avoided until the film has dissolved.

A BELBUCA film, if chewed or swallowed, may result in lower peak concentrations and lower bioavailability than when used as directed.

Demonstrate proper administration technique to the patient [see *Patient Counseling Information (17)*].

3 DOSAGE FORMS AND STRENGTHS

Dosage strengths of BELBUCA are based on the active moiety, buprenorphine.

The 75 mcg dosage form is a buccal film that contains 75 mcg buprenorphine. The film is white on one side, with E0 printed in black, and yellow on the other side.

The 150 mcg dosage form is a buccal film that contains 150 mcg buprenorphine. The film is white on one side, with E1 printed in black, and yellow on the other side.

The 300 mcg dosage form is a buccal film that contains 300 mcg buprenorphine. The film is white on one side, with E3 printed in black, and yellow on the other side.

The 450 mcg dosage form is a buccal film that contains 450 mcg buprenorphine. The film is white on one side, with E4 printed in black, and yellow on the other side.

The 600 mcg dosage form is a buccal film that contains 600 mcg buprenorphine. The film is white on one side, with E6 printed in black, and yellow on the other side.

The 750 mcg dosage form is a buccal film that contains 750 mcg buprenorphine. The film is white on one side, with E7 printed in black, and yellow on the other side.

The 900 mcg dosage form is a buccal film that contains 900 mcg buprenorphine. The film is white on one side, with E9 printed in black, and yellow on the other side.

4 CONTRAINDICATIONS

BELBUCA 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)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [*see Warnings and Precautions (5.15)*]
- Hypersensitivity (e.g., anaphylaxis) to buprenorphine [*see Warnings and Precautions (5.13)*, *Adverse Reactions (6)*]

5 WARNINGS AND PRECAUTIONS

5.1 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 [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BELBUCA. Addiction can occur at recommended dosages and if the drug is misused or abused.

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 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 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. Consider prescribing naloxone for the emergency treatment of opioid overdose [*see Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*].

Abuse or misuse of BELBUCA by swallowing may cause choking, overdose, and death [*see Overdosage (10)*].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing BELBUCA. 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 [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.opioidanalgesicrems.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 BELBUCA, the risk is greatest during initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression when initiating therapy with BELBUCA and following dosage increases.

To reduce the risk of respiratory depression, proper dosing and titration of BELBUCA are essential [see *Dosage and Administration (2)*]. 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.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see *Patient Counseling Information (17)*].

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)*].

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with BELBUCA. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered [see *Patient Counseling Information (17)*].

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone [see *Warnings and Precautions (5.1, 5.5)*, *Patient Counseling Information (17)*].

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of BELBUCA 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 due to Interactions with Benzodiazepines or Other Central Nervous System Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of BELBUCA 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.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*].

Advise both patients and caregivers about the risks of respiratory depression and sedation when BELBUCA 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)*].

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

The use of BELBUCA 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: BELBUCA-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with 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 BELBUCA [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 as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating BELBUCA and when BELBUCA 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 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.

5.8 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 [see *Dosage and Administration (2.4)*, *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.2)*].

5.9 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 (e.g., phenothiazines or general anesthetics) [see *Drug Interactions (7)*]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of BELBUCA. In patients with circulatory shock, BELBUCA may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of BELBUCA in patients with circulatory shock.

5.10 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), BELBUCA 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 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.

5.11 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. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injection drug abuse may have played a causative or contributory role. For patients at increased risk of hepatotoxicity (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.

5.12 Risk of Overdose in Patients with Moderate to Severe Hepatic Impairment

In a pharmacokinetic study in 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 [see *Dosage and Administration (2.6)*, *Use in Specific Populations (8.6)*].

5.13 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. BELBUCA is contraindicated in patients with a history of hypersensitivity to buprenorphine.

5.14 Withdrawal

Do not abruptly discontinue BELBUCA in a patient physically dependent on opioids. When discontinuing BELBUCA in a physically dependent patient, gradually taper the dosage. Rapid tapering of buprenorphine 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, the use of BELBUCA, a partial agonist opioid analgesic, in patients who are receiving a full opioid agonist analgesic may reduce the analgesic effect and/or precipitate withdrawal symptoms. Avoid concomitant use of BELBUCA with a full opioid agonist analgesic.

5.15 Risk of Use in Patients with Gastrointestinal Conditions

BELBUCA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

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.

5.16 Increased Risk of Seizures in Patients with Seizure Disorders

The buprenorphine in BELBUCA 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.

5.17 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 higher plasma levels of the opioid. For patients with known or suspected mucositis, a dose reduction is recommended. Monitor these patients carefully for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine [see *Dosage and Administration (2.7)*, *Clinical Pharmacology (12.3)*].

5.18 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.

6 ADVERSE REACTIONS

The following serious adverse reactions described elsewhere in the labeling include:

- 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 Benzodiazepines and Other CNS Depressants [see *Warnings and Precautions (5.5)*]
- Adrenal Insufficiency [see *Warnings and Precautions (5.7)*]
- QTc Prolongation [see *Warnings and Precautions (5.8)*]
- Severe Hypotension [see *Warnings and Precautions (5.9)*]
- Hepatotoxicity [see *Warnings and Precautions (5.11)*]
- Anaphylactic/Allergic Reactions [see *Warnings and Precautions (5.13)*]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions (5.15)*]
- Seizures [see *Warnings and Precautions (5.16)*]

6.1 Clinical Trial 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 2,127 patients were treated with BELBUCA in controlled and open-label chronic pain trials. There were 504 patients treated for approximately six months and 253 patients treated for approximately one year. The clinical trial population consisted of patients with chronic moderate-to-severe pain.

The most common serious adverse drug reactions (all $\leq 0.2\%$) occurring during clinical trials with BELBUCA were: cellulitis, pneumonia, ileus, atrial fibrillation, coronary artery disease, cerebrovascular accident, syncope, transient ischemic attack, chest pain, non-cardiac chest pain, ankle fracture, cholecystitis, osteoarthritis, and dehydration.

The most common adverse events ($\geq 2\%$) leading to discontinuation were nausea, vomiting, and liver function test abnormality.

The most common adverse events ($\geq 5\%$) reported by opioid-naïve, opioid-experienced, and overall patients exposed to BELBUCA in clinical trials and compared against placebo are shown in [Table 2](#), [Table 3](#) and [Table 4](#):

Table 2: Adverse Events Reported in $\geq 5\%$ of Patients during the Open-Label Titration Phase and Double-Blind Treatment Phase of Controlled Studies: Opioid-Naïve Patients

MedDRA Preferred Term	Open-Label Titration Phase	Double-Blind Treatment Phase	
	BELBUCA (N=749)	BELBUCA (N=229)	Placebo (N=232)
Nausea	50%	10%	7%
Constipation	13%	4%	3%
Vomiting	8%	4%	<1%
Headache	8%	2%	3%
Dizziness	6%	2%	<1%
Somnolence	7%	1%	<1%
Fatigue	5%	0%	1%

Table 3: Adverse Events Reported in $\geq 5\%$ of Patients during the Open-Label Titration Phase and Double-Blind Treatment Phase of Controlled Studies: Opioid-Experienced Patients

MedDRA Preferred Term	Open-Label Titration Phase	Double-Blind Treatment Phase	
	BELBUCA (N=810)	BELBUCA (N=254)	Placebo (N=256)
Nausea	17%	7%	7%
Constipation	8%	3%	1%
Vomiting	7%	5%	2%
Headache	7%	2%	3%

MedDRA Preferred Term	Open-Label Titration Phase	Double-Blind Treatment Phase	
	BELBUCA (N=810)	BELBUCA (N=254)	Placebo (N=256)
Dizziness	5%	2%	<1%
Somnolence	5%	1%	<1%
Drug Withdrawal Syndrome	0%	4%	10%

Table 4: Adverse Events Reported in $\geq 5\%$ of Patients during the Open-Label Titration Phase and Double-Blind Treatment Phase of Controlled Studies

MedDRA Preferred Term	Open-Label Titration Phase	Double-Blind Treatment Phase	
	BELBUCA (N=1889)	BELBUCA (N=600)	Placebo (N=606)
Nausea	33%	9%	8%
Constipation	11%	4%	2%
Vomiting	7%	5%	2%
Headache	8%	4%	3%
Dizziness	6%	2%	<1%
Somnolence	6%	<1%	<1%
Drug Withdrawal Syndrome	1%	2%	5%

The most common ($\geq 5\%$), common ($\geq 1\%$ to $< 5\%$), and least common ($< 1\%$) adverse reactions reported by patients taking BELBUCA in the controlled and open-label clinical studies are presented below:

Most common adverse reactions ($\geq 5\%$): nausea, constipation, headache, vomiting, fatigue, dizziness, and somnolence.

Common ($\geq 1\%$ to $< 5\%$) adverse reactions (organized by MedDRA [Medical Dictionary for Regulatory Activities] System Organ Class):

Blood and lymphatic system disorders: anemia

Gastrointestinal disorders: abdominal pain, diarrhea, dry mouth

General disorders and administration site conditions: peripheral edema, pyrexia, drug withdrawal syndrome

Infections and infestations: upper respiratory tract infection, urinary tract infection, nasopharyngitis, sinusitis, bronchitis, gastroenteritis

Injury, poisoning, and procedural complications: contusion, fall

Metabolism and nutrition disorders: decreased appetite

Musculoskeletal and connective tissue disorders: muscle spasms, back pain

Psychiatric disorders: anxiety, insomnia, depression

Respiratory, thoracic and mediastinal disorders: oropharyngeal pain, sinus congestion

Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus, rash

Vascular disorders: hot flush, hypertension

Least common (<1%) adverse reactions:

Abdominal discomfort, acute sinusitis, dyspepsia, toothache, asthenia, chills, cellulitis, tooth abscess, excoriation, laceration, aspartate aminotransferase increased, blood pressure increased, blood testosterone decreased, electrocardiogram QT prolonged, liver function test abnormal, musculoskeletal pain, neck pain, hypoesthesia, lethargy, migraine, tremor, cough, dyspnea, nasal congestion, rhinorrhea.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of buprenorphine. 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 BELBUCA.

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

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with BELBUCA.

Table 5: Clinically Significant Drug Interactions

Benzodiazepines	
<i>Clinical Impact:</i>	There have been a number of reports regarding coma and death associated with the misuse and abuse of the combination of buprenorphine and benzodiazepines. In many, but not all of these cases, buprenorphine was misused by self-injection of crushed buprenorphine tablets. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists.
<i>Intervention:</i>	Closely monitor patients with concurrent use of BELBUCA and benzodiazepines. Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking BELBUCA, and warn patients to use benzodiazepines concurrently with BELBUCA only as directed by their physician.
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. If concomitant use is

	warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see <i>Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3, 5.5)</i>].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, alcohol.
Inhibitors of CYP3A4	
<i>Clinical Impact:</i>	The concomitant use of buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of BELBUCA is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the buprenorphine plasma concentration will decrease [see <i>Clinical Pharmacology (12.3)</i>], potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to buprenorphine.
<i>Intervention:</i>	If concomitant use is necessary, consider dosage reduction of BELBUCA until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the BELBUCA dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
<i>Examples:</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
<i>Clinical Impact:</i>	The concomitant use of buprenorphine and CYP3A4 inducers can decrease the plasma concentration of buprenorphine [see <i>Clinical Pharmacology (12.3)</i>], potentially resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to buprenorphine. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the buprenorphine plasma concentration will increase [see <i>Clinical Pharmacology (12.3)</i>], which could increase or prolong both therapeutic effects and adverse reactions and may cause serious respiratory depression.
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the BELBUCA dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider BELBUCA dosage reduction and monitor for signs of respiratory depression.
<i>Examples:</i>	Rifampin, carbamazepine, phenytoin
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 BELBUCA 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 opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.3)</i>].
<i>Intervention:</i>	The use of BELBUCA is not recommended for 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 BELBUCA and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine
Muscle Relaxants	
<i>Clinical Impact:</i>	Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients receiving muscle relaxants and BELBUCA for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of BELBUCA and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose [see <i>Dosage and Administration (2.2)</i> , <i>Warnings and Precautions (5.3, 5.5)</i>].
<i>Examples:</i>	cyclobenzaprine, metaxalone
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 the 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 BELBUCA is used concomitantly with anticholinergic drugs.
Antiretrovirals: Nucleoside reverse transcriptase inhibitors (NRTIs)	
<i>Clinical Impact:</i>	Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected.
<i>Intervention:</i>	None
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
<i>Clinical Impact:</i>	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A inducers, whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.
<i>Intervention:</i>	Patients who are on chronic BELBUCA treatment should have their dose monitored if NNRTIs are added to their treatment regimen.

<i>Examples:</i>	efavirenz, nevirapine, etravirine, delavirdine
Antiretrovirals: Protease inhibitors (PIs)	
<i>Clinical Impact:</i>	Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetics and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine, and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly.
<i>Intervention:</i>	Monitor patients taking BELBUCA and atazanavir with and without ritonavir and reduce the dose of BELBUCA if warranted.
<i>Examples:</i>	atazanavir, ritonavir

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [*see Warnings and Precautions (5.4)*]. There are no adequate and well-controlled studies of BELBUCA or buprenorphine in pregnant women. Limited published data on use of buprenorphine, the active ingredient in BELBUCA, in pregnancy, have not shown an increased risk of major malformations. Reproductive and developmental studies in rats and rabbits identified adverse events at approximately 2 times the maximum recommended human dose (MRHD) of 1.8 mg/day of BELBUCA. Embryofetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis at doses approximately 54 and 2.2 times, respectively, the MRHD of 1.8 mg/day of buprenorphine. Pre- and postnatal development studies in rats demonstrated increased neonatal deaths at 2.7 times and above and dystocia at approximately 27 times the MRHD of 1.8 mg/day of buprenorphine. No clear teratogenic effects were seen when buprenorphine was administered during organogenesis with a range of doses 5 times or greater than the MRHD of 1.8 mg/day of buprenorphine. However, increases in skeletal abnormalities were noted in rats and rabbits administered buprenorphine daily during organogenesis at doses approximately 5.4 and 10.8 times the MRHD of 1.8 mg/day of buprenorphine, respectively. In a few studies, some events such as acephalus and omphalocele were also observed but these findings were not clearly treatment-related [*see Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy can occur regardless of the health of the mother or the use of medications. 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. BELBUCA is not recommended for use in women immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including BELBUCA, 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.

Data

Animal Data

The exposure margins listed below are based on body surface area comparisons (mg/m^2) to MRHD of 1.8 mg buprenorphine via BELBUCA.

Following oral administration to rats no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day (estimated exposure approximately 1351 times the MRHD of 1.8 mg). Following oral administration to rabbits, no teratogenic effects were observed at buprenorphine doses up to 40 mg/kg/day (estimated exposure approximately 432 times the MRHD of 1.8 mg). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 161 times and 324 times, respectively, the MRHD of 1.8 mg). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 54 times the MRHD of 1.8 mg).

In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 27 and 54 times, respectively, the MRHD of 1.8 mg), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 4.3 and 8.7 times, respectively, the MRHD of 1.8 mg), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 865 times the MRHD of 1.8 mg) and 25 mg/kg/day in rabbits (estimated exposure was approximately 270 times the MRHD of 1.8 mg). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 5.4 times the MRHD of 1.8 mg), but were not observed at oral doses up to 160 mg/kg/day.

Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 54 times the MRHD of 1.8 mg) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately 10.8 times the MRHD of 1.8 mg) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 2.2 times the MRHD of 1.8 mg).

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine during gestation and lactation at 5 mg/kg/day (approximately 27 times the MRHD of 1.8 mg). Fertility, pre-, and post-natal development studies

with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 4.3 times the MRHD of 1.8 mg), after IM doses of 0.5 mg/kg/day and up (approximately 2.7 times the MRHD of 1.8 mg), and after SC doses of 0.1 mg/kg/day and up (approximately 0.5 times the MRHD of 1.8 mg). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 432 times the MRHD of 1.8 mg).

8.2 Lactation

Risk Summary

Based on two studies in 13 lactating women being treated for opioid dependence and their breastfed infants, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants [see *Data*]. There are no data on the effects of BELBUCA on milk production. 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 BELBUCA.

Clinical Considerations

Monitor infants exposed to BELBUCA through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of buprenorphine is stopped or when breastfeeding is stopped.

Data

Based on limited data from a study of six lactating women being treated for opioid dependence who were taking a median oral dose of buprenorphine of 0.29 mg/kg/day 5-8 days after delivery, breast milk contained a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, which are equal to 0.2% and 0.12% of the maternal weight-adjusted dose. The median concentrations of buprenorphine and norbuprenorphine in infant urine were 1.0 nmol/L and 2.3 nmol/L, respectively.

Based on limited data from a study of seven lactating women being treated for opioid dependence who were taking a median oral dose of buprenorphine of 7 mg/day an average of 1.12 months after delivery, the mean milk concentrations of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L, respectively. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, which are 0.38% and 0.18% of the maternal weight-adjusted dose.

No adverse reactions were observed in the infants in these two studies.

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 *Clinical Pharmacology (12.2)*, *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and efficacy of BELBUCA have not been established in pediatric patients.

8.5 Geriatric Use

Of the total number of patients that were treated with BELBUCA in controlled and open-label chronic pain trials (2,127), 340 patients were 65 years and older. Of those, 49 patients were aged 75 years and older. The incidences of selected BELBUCA-related adverse effects were higher in older subjects.

No notable differences in pharmacokinetics were observed from population pharmacokinetic analysis in subjects aged 65 and older compared to younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between the elderly and younger patients. Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, use caution in the elderly population to ensure safe use. Titrate the dosage of BELBUCA slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [*see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)*].

Buprenorphine 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

BELBUCA has not been evaluated in patients with severe hepatic impairment.

The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a pharmacokinetic study. Buprenorphine is extensively metabolized in the liver and 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.

Given that increased buprenorphine plasma levels are associated with a greater risk of toxicity and overdose, a dosage reduction in patients with severe hepatic impairment (i.e., Child-Pugh C) is recommended [*see Dosage and Administration (2.6)*]. Monitor patients with severe hepatic impairment for signs and symptoms of overdose. A dosage reduction in patients with moderate hepatic impairment (Child-Pugh B) is not needed; however, monitor these patients for signs and symptoms of toxicity or overdose. A dosage reduction in patients with mild hepatic impairment (Child-Pugh A) is not needed [*see Dosage and Administration (2.6), Warnings and Precautions (5.11), Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

BELBUCA contains buprenorphine hydrochloride, a Schedule III controlled substance.

9.2 Abuse

BELBUCA contains buprenorphine, a substance with a potential for abuse similar to other Schedule III opioids. BELBUCA can be abused and is subject to misuse, abuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1)*].

All patients treated with opioids, including BELBUCA, require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carry 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 providers. “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 persons with substance use disorders. In addition, abuse of opioids can occur in the absence of true addiction.

BELBUCA, 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 BELBUCA

BELBUCA is intended for buccal use only. Abuse of BELBUCA poses a risk of overdose and death. This risk is increased with concurrent abuse of BELBUCA with alcohol and other substances, including other opioids and benzodiazepines [*see Warnings and Precautions (5.5), Drug Interactions (7)*]. Intentional compromise of the buccal film might result in the uncontrolled delivery of buprenorphine and pose a significant risk to the abuser that could result in overdose and death [*see Warnings and Precautions (5.1)*]. Abuse may occur by applying the buccal film in the absence of legitimate purpose, or by swallowing, snorting, or injecting buprenorphine extracted from the buccal film. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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), or mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue BELBUCA in a patient physically dependent on opioids. Rapid tapering of BELBUCA 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 BELBUCA, gradually taper the dosage using a patient-specific plan that considers the following: the dose of BELBUCA 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 (5.14)*].

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 BELBUCA is 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 re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema, as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. However, naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. High doses of naloxone, 10-35 mg/70 kg, may be of limited value in the management of buprenorphine overdose. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride (a respiratory stimulant) has also been used.

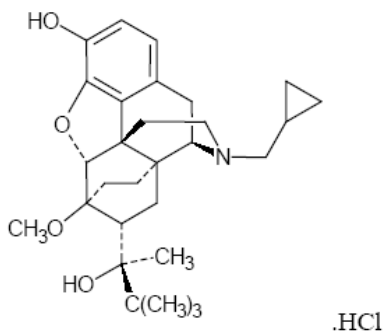
Because the duration of reversal would be expected to be less than the duration of action of buprenorphine from BELBUCA, carefully monitor the patient until spontaneous respiration is reliably re-established. Even in the face of improvement, continued medical monitoring is required for at least 24 hours because of the possibility of extended effects of buprenorphine.

In an individual physically dependent on opioids, administration of an opioid receptor antagonist may precipitate an acute withdrawal. 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 begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

BELBUCA is a buccal film that provides transmucosal delivery of buprenorphine, a partial opioid agonist. BELBUCA is a rectangular bi-layer, peppermint-flavored, buccal film with rounded corners, consisting of a white to off-white backing layer with strength identifier printed in black ink and a light yellow to yellow active mucoadhesive layer containing buprenorphine hydrochloride. The yellow side of the film is applied to the inside of the cheek where it adheres to the moist buccal mucosa to deliver the drug as the film dissolves.

Buprenorphine hydrochloride USP is the active ingredient in BELBUCA. The chemical name of buprenorphine hydrochloride is 6,14-ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4, 5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-, hydrochloride, [5 α , 7 α , (S)]. Its structural formula is as follows:



The molecular weight of buprenorphine hydrochloride is 504.10; the empirical formula is C₂₉H₄₁NO₄·HCl. Buprenorphine hydrochloride occurs as a white or off-white crystalline powder. It is sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane. The pKa is 8.5 for the amine function and 10.0 for the phenol function.

Dosage strengths of BELBUCA are based on the active moiety, buprenorphine. BELBUCA is available as 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg buprenorphine per film. The strength of each film is dependent on the buprenorphine concentration in the formulation and the surface area of the film. [Table 6](#) lists the dosage strength, equivalent amount of buprenorphine hydrochloride USP (active ingredient), unique identifier and film size for each strength.

Table 6: BELBUCA Identifier and Film Size

Buprenorphine Strength (mcg)	Buprenorphine Hydrochloride (mcg)	BELBUCA Identifier	Film Size (cm ²)
75	80.9	E0	1.215
150	161.8	E1	2.431
300	323.4	E3	0.934
450	485.1	E4	1.400
600	646.8	E6	1.867
750	808.5	E7	2.334
900	970.2	E9	2.801

Each buccal film also contains carboxymethylcellulose sodium USP, citric acid anhydrous USP, hydroxyethylcellulose NF, hydroxypropylcellulose NF, methylparaben NF, monobasic sodium phosphate anhydrous USP, peppermint oil NF, polycarbophil USP, propylene glycol USP, propylparaben NF, sodium benzoate NF, sodium hydroxide NF, saccharin sodium NF, titanium dioxide USP, vitamin E acetate USP, yellow iron oxide, purified water USP, and TekPrint SW-9008 black ink (shellac NF, black iron oxide NF).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor.

12.2 Pharmacodynamics

Effects on the Central Nervous System

The principal action of therapeutic value of buprenorphine is analgesia and is thought to be due to buprenorphine binding with high affinity to opioid receptors on neurons in the brain and spinal cord.

Buprenorphine produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Buprenorphine 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 worsening hypoxia in the setting of buprenorphine overdose.

Unlike other opioids, buprenorphine appears to exhibit a dose-ceiling effect.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Buprenorphine causes a reduction in motility associated with an increase in tone in 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. Buprenorphine may cause an increase in biliary tract pressure as a result of spasm of the sphincter of Oddi. 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

Buprenorphine produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on Cardiac Electrophysiology

QTc prolongation with BELBUCA has been observed. Of the 1590 patients that were treated with BELBUCA in controlled and open-label chronic pain trials at doses up to 900 mcg every 12 hours, 2% demonstrated a prolongation of QTcF to a post-baseline value between 450 - 480 msec during therapy.

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 varies widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of buprenorphine 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, 2.4)].

Concentration–Adverse Reaction Relationships

There is a relationship between increasing buprenorphine 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, 2.3, 2.4)].

12.3 Pharmacokinetics

Absorption

Systemic plasma levels of buprenorphine increased in a linear manner (C_{max} and AUC) over the single dose range of 75 to 1200 mcg as shown in Table 7. The absolute bioavailability of BELBUCA ranged from 46 to 65%.

Table 7: Mean (\pm SD) BELBUCA Pharmacokinetic Parameters

Regimen	Dosage (mcg)	C_{max} (ng/mL)	AUC _{0-t} (h·ng/mL)	AUC _{0-∞} (h·ng/mL)	T_{max}^* (hr)
Single Dose	75	0.17±0.30	0.46±0.22	0.63±0.24	3.00 (1.50-4.00)
	300	0.47±0.47	2.00±0.68	2.3±0.68	2.50 (0.50-4.00)
	1200	1.43±0.45	9.6±2.9	10.5±3.32	3.00 (1.00-4.00)

* T_{max} values reported as median and range

Following the multiple dose administration (60 to 240 mcg every 12 hours) of BELBUCA, apparent steady-state buprenorphine plasma concentrations were achieved prior to the 6th dose. Buprenorphine steady-state C_{max} and AUC increased proportional to dose.

Systemic exposure to buprenorphine from BELBUCA film was reduced by 23-27% by the ingestion of liquids (cold, hot and room temperature water) during film administration; additionally, coadministration with low pH liquid, such as decaffeinated cola, decreased buprenorphine exposure from BELBUCA by approximately 37%. The consumption of liquids should be avoided until the buccal film has completely dissolved [see *Dosage and Administration* (2.8)].

Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Elimination

Metabolism

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind to opioid receptors *in vitro*; however, it has not been studied clinically for opioid-like activity.

Excretion

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine was free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Based on multiple-dose studies performed with BELBUCA, the mean plasma elimination half-life of buprenorphine was 27.6 ± 11.2 hours.

Drug Interaction Studies

CYP3A4 Inhibitors and Inducers

Buprenorphine undergoes N-dealkylation mediated primarily by CYP3A4, so its metabolism can be inhibited by CYP3A4 inhibitors. The interaction of buprenorphine with all CYP3A4 inducers has not been studied [see *Drug Interactions (7)*].

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in *in vitro* studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

Specific Populations

Age: Geriatric Patients

No notable differences in pharmacokinetics were observed from population PK analysis in subjects aged 65 and older compared to younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between the elderly and younger patients.

Sex

No notable sex differences in pharmacokinetics were observed from population PK analysis.

Renal Impairment

No studies in patients with renal impairment have been performed with BELBUCA. In an independent study, the effect of impaired renal function on buprenorphine pharmacokinetics after IV bolus and after continuous IV infusion administration was evaluated and no notable differences in plasma buprenorphine concentrations were identified in patients with normal renal function compared to impaired renal function or renal failure.

Hepatic Impairment

BELBUCA has not been evaluated in patients with severe hepatic impairment. The pharmacokinetics of buprenorphine following an IV infusion of 0.3 mg of buprenorphine were compared in 8 patients with mild hepatic impairment (Child-Pugh A), 4 patients with moderate impairment (Child-Pugh B), and 12 subjects with normal hepatic function. Buprenorphine and norbuprenorphine plasma levels did not increase in mild or moderately impaired patient cohorts.

In another pharmacokinetic study, the disposition of buprenorphine was determined after administering a 2.0/0.5 mg buprenorphine/naloxone sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function. In subjects with mild hepatic impairment, the changes in mean C_{max} , AUC_{0-last} , and half-life values of buprenorphine were not clinically significant. No dose adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean C_{max} , AUC_{0-last} , and half-life values of buprenorphine were increased (Table 8) [see Dosage and Administration (2.6), Warnings and Precautions (5.11), Use in Specific Populations (8.6)].

Table 8: Changes in Pharmacokinetic Parameters in Subjects with Moderate and Severe Hepatic Impairment

Hepatic Impairment	PK Parameters	Increase in buprenorphine compared to healthy subjects
Moderate	C_{max}	8%
	AUC_{0-last}	64%
	Half-life	35%
Severe	C_{max}	72%
	AUC_{0-last}	181%
	Half-life	57%

Oral Mucositis

In an open-label pharmacokinetic study in 6 cancer patients with Grade 3 mucositis, buprenorphine was absorbed more rapidly from BELBUCA resulting in a higher C_{max} (~79%) and AUC (~56%) compared to age- and gender-matched healthy control subjects [see Dosage and Administration (2.7), Warnings and Precautions (5.17)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day for 27 months (estimated exposure was approximately 3, 29, and 299 times the maximum recommended human dose (MRHD) of buccal BELBUCA of 1.8 mg on a mg/m² basis, respectively). Statistically significant dose-related increases in testicular interstitial (Leydig's) cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 267 times the MRHD).

Mutagenesis

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [³H]thymidine, and positive in an unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure approximately 427 times the MRHD) or up to 5 mg/kg/day IM or SC (estimated exposure was approximately 27 times the MRHD).

14 CLINICAL STUDIES

The efficacy of BELBUCA has been evaluated in three 12-week double-blind, placebo-controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate-to-severe chronic low back pain using pain scores as the primary efficacy variable. Two of these studies, described below, demonstrated efficacy in patients with low back pain. One study in low back pain did not show a statistically significant pain reduction for BELBUCA compared to placebo.

12-Week Study in Opioid-Naïve Patients with Chronic Low Back Pain

A total of 749 patients with chronic low back pain entered an open-label, dose-titration period for up to eight weeks. Potential subjects were excluded from participation for QTcF interval of 450 ms or more, hypokalemia, clinically unstable cardiac disease, a history of Long QT Syndrome or an immediate family member with this condition, or taking Class IA or Class III antiarrhythmic medications. Patients initiated therapy with a single 75 mcg dose of BELBUCA on Day 1 and continued taking BELBUCA 75 mcg either once daily or every 12 hours for 4-8 days as tolerated. The dose was then increased to 150 mcg every 12 hours, and patients could continue to dose escalate in 150 mcg dose increments every 4-8 days for up to 6 weeks if the adverse effects were tolerable and the analgesic effects were not adequate. Patients who achieved adequate analgesia and tolerable adverse effects on BELBUCA for at least 2 weeks were then randomized to continue their titrated dose of BELBUCA or matching placebo buccal film. Sixty-one percent (61%) of the patients who entered the open-

label dose titration period were able to titrate to a tolerable and effective dose and were randomized into a 12-week, double-blind treatment period. Fifteen percent of patients discontinued due to an adverse event and 4% discontinued due to lack of a therapeutic effect. The remaining 20% of patients discontinued due to various non-drug related administrative reasons.

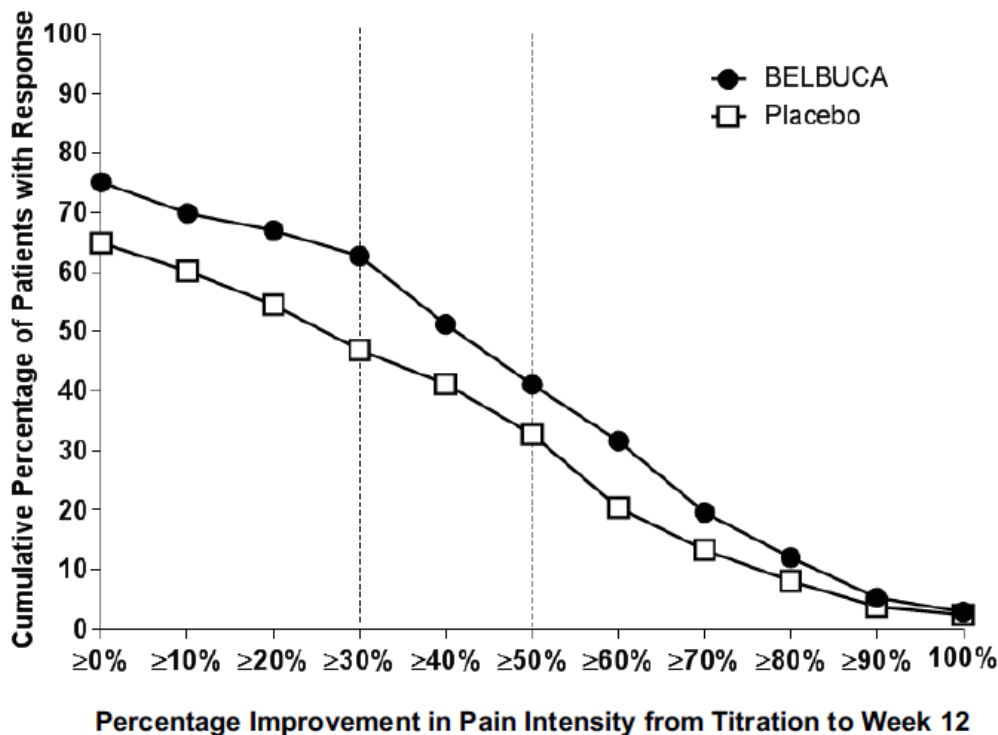
During the first 2 weeks of double-blind treatment, patients were allowed up to 2 tablets per day of hydrocodone/acetaminophen 5/325 mg as supplemental analgesia to minimize opioid withdrawal symptoms in patients randomized to placebo. Thereafter, the supplemental analgesia was limited to 1 to 2 tablets of acetaminophen 500 mg per day. Seventy-six percent of the patients treated with BELBUCA completed the 12-week treatment compared to 73% of the patients treated with placebo. Of the 209 patients randomized to BELBUCA, 4% discontinued due to lack of efficacy and 8% due to adverse events. Of the 211 patients randomized to placebo, 11% discontinued due to lack of efficacy and 4% due to adverse events.

Of the patients who were randomized, the mean pain (SD) scores on a 0 to 10 numeric rating scale (NRS) were 7.1 (1.06) and 7.2 (1.05) prior to open-label titration and 2.8 (1.01) and 2.8 (1.12) at the beginning of the double-blind period for BELBUCA and placebo, respectively. The change from double-blind baseline to week 12 in mean pain (SD) NRS score was statistically significant favoring patients treated with BELBUCA compared with patients treated with placebo.

A higher proportion of BELBUCA patients (62%) had at least a 30% reduction in pain score from prior to open-label titration to study endpoint when compared to patients who received placebo buccal film (47%). A higher proportion of BELBUCA patients (41%) also had at least a 50% reduction in pain score from prior to open-label titration to study endpoint compared to patients who received placebo (33%).

The proportion of patients with various degrees of improvement, from prior to open-label titration (Titration-Baseline) to study endpoint, is shown in Figure 1.

Figure 1: Percentage Improvement in Pain Intensity from Titration-Baseline to Week 12



12-Week Study in Opioid-Experienced Patients with Chronic Low Back Pain

Eight hundred and ten (810) patients on chronic opioid therapy (total daily dose 30-160 mg in oral morphine sulfate equivalents (MSE) for at least 4 weeks) entered an open-label, dose-titration period with BELBUCA for up to 8 weeks, following taper of their prior opioids to 30 mg oral MSE daily. Potential subjects were excluded from participation for QTcF interval of 450 ms or more, hypokalemia, clinically unstable cardiac disease, a history of Long QT Syndrome or an immediate family member with this condition, or taking Class IA or Class III antiarrhythmic medications. Patients were initiated with BELBUCA 150 mcg every 12 hours if they were on 30 to 89 mg oral MSE daily and 300 mcg every 12 hours if they were on 90 to 160 mg oral MSE daily prior to taper. If a patient tolerated the adverse events and the analgesic effects were not adequate, the dose was increased in increments of 150 mcg every 12 hours after 4 to 8 days for up to 6 weeks. Patients were permitted to take hydrocodone/acetaminophen 5/325 mg as analgesic rescue as needed up to a maximum of 4 doses per day during the open-label dose titration period. After a dose was reached with adequate analgesia and tolerable adverse effects for a period of 2 weeks, patients were randomized to continue their titrated dose of BELBUCA or matching placebo. Sixty-three percent (63%) of the patients who entered the open-label titration period were able to titrate to a tolerable and effective dose and were randomized into a 12-week double-blind treatment phase. Ten percent (10%) of patients discontinued due to an adverse event, 8% discontinued due to lack of a therapeutic effect, and 0.1% discontinued due to opioid withdrawal during the open-label titration period. The remaining 20% of patients discontinued due to various non-drug related administrative reasons.

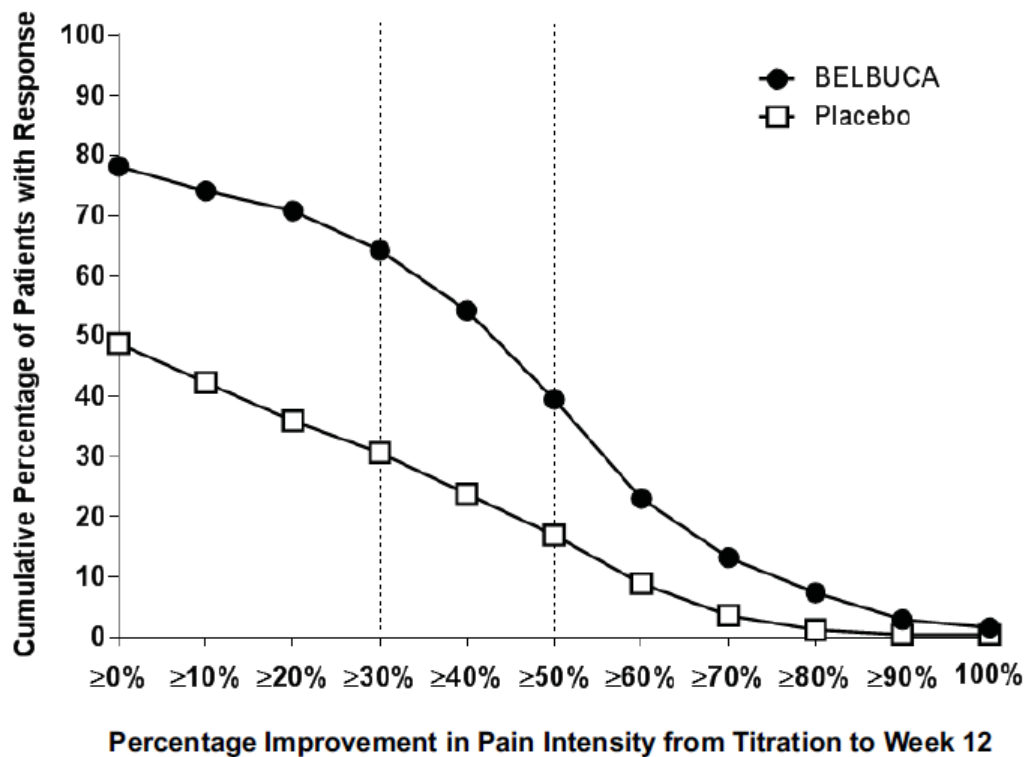
During the double-blind period, patients were permitted to take up to 2 doses of 5/325 mg or 10/650 mg of hydrocodone/acetaminophen per day for the first 2 weeks to minimize opioid withdrawal symptoms in patients randomized to placebo. After the first 2 weeks, patients were permitted to take 1 dose of 5/325 mg or 10/650 mg per day. Eighty-three percent of patients treated with BELBUCA and 57% of patients treated with placebo buccal film completed the 12-week treatment period. Of the 243 patients randomized to BELBUCA, 8% discontinued due to lack of efficacy and 2% due to adverse events. Of the 248 patients randomized to placebo buccal film, 25% discontinued due to lack of efficacy and 5% due to adverse events.

Of the patients who were randomized into the double-blind period, the mean pain (SD) NRS scores were 6.8 (1.28) and 6.6 (1.32) prior to open-label titration and 2.9 (0.985) and 2.8 (1.05) at the beginning of the double-blind period for BELBUCA and placebo, respectively. The change from baseline to week 12 in mean pain (SD) NRS score was statistically significant in favor of patients treated with BELBUCA compared with patients treated with placebo.

A higher proportion of BELBUCA patients (64%) had at least a 30% reduction in pain score from prior to open-label titration to study endpoint when compared to patients who received placebo buccal film (31%). A higher proportion of BELBUCA patients (39%) also had at least a 50% reduction in pain score from prior to open-label titration to study endpoint compared to patients who received placebo (17%).

The proportion of patients with various degrees of improvement from prior to open-label titration (Titration-Baseline) to study endpoint is shown in [Figure 2](#).

Figure 2: Percentage Improvement in Pain Intensity from Titration-Baseline to Week 12



16 HOW SUPPLIED/STORAGE AND HANDLING

BELBUCA (buprenorphine buccal film) films are supplied in cartons containing 60 individual child-resistant foil packages as follows:

Strength	NDC Number Carton	NDC Number Foil Package	Foil Color
The 75 mcg buccal film is printed with E0	59385-021-60	59385-021-01	Red
The 150 mcg buccal film is printed with E1	59385-022-60	59385-022-01	Green
The 300 mcg buccal film is printed with E3	59385-023-60	59385-023-01	Gray
The 450 mcg buccal film is printed with E4	59385-024-60	59385-024-01	Purple
The 600 mcg buccal film is printed with E6	59385-025-60	59385-025-01	Blue
The 750 mcg buccal film is printed with E7	59385-026-60	59385-026-01	Light Blue
The 900 mcg buccal film is printed with E9	59385-027-60	59385-027-01	Orange

Store at 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F).

Store BELBUCA 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).

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store BELBUCA 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 (5.1, 5.3)*, *Drug Abuse and Dependence (9.2)*]. Inform patients that leaving BELBUCA 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 BELBUCA should be disposed of by removing the BELBUCA film from the foil packaging and 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 BELBUCA, even when taken as recommended, can result in addiction, abuse, and misuse, which could lead to overdose and death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share BELBUCA with others and to take steps to protect BELBUCA 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 BELBUCA or when the dosage is increased, and that it can occur even at recommended doses.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see *Warnings and Precautions (5.3)*].

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with BELBUCA. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*].

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered [see *Overdosage (10)*].

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Accidental Exposure

Inform patients that accidental exposure, especially in children, may result in respiratory depression or death [*see Warnings and Precautions (5.3)*].

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if BELBUCA 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 BELBUCA 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)*].

Adrenal Insufficiency

Inform patients that BELBUCA 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 (5.7)*].

Interaction with Benzodiazepines

Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking BELBUCA, and warn patients to use benzodiazepines concurrently with BELBUCA only as directed by their physician [*see Drug Interactions (7)*].

Important Administration Instructions

Instruct patients how to properly use BELBUCA, including the following:

- To carefully follow instructions for the application of BELBUCA and to avoid eating or drinking until it dissolves.
- To apply BELBUCA once daily, or every twelve (12) hours at the same time or times each day.
- To avoid applying BELBUCA to areas of the mouth with any open sores or lesions.
- To not use BELBUCA if the pouch seal is broken or the buccal film is cut, damaged, or changed in any way.

Important Discontinuation Instructions

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

Hypotension

Inform patients that BELBUCA 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 BELBUCA. Advise patients how to recognize such a reaction and when to seek medical attention [*see Warnings and Precautions (5.13)*].

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of BELBUCA 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)*].

Embryofetal Toxicity

Advise female patients that BELBUCA 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 BELBUCA [*see Use in Specific Populations (8.2)*].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [*see Adverse Reactions (6), Clinical Pharmacology (12.2)*].

Driving or Operating Heavy Machinery

Inform patients that BELBUCA 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 (5.18)*].

Healthcare professionals can telephone BioDelivery Sciences International, Inc. at 1-800-469-0261 or access www.BELBUCA.com for information on this product.

Distributed by:

BioDelivery Sciences International, Inc.
Raleigh, NC 27612 USA

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BEL-001-PI-Mar2021

Medication Guide
BELBUCA® (bel-BUE-kuh)
(buprenorphine buccal film), CIII

BELBUCA 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 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 BELBUCA:

- **Get emergency help or call 911 right away if you take too much BELBUCA (overdose).** When you first start taking BELBUCA, 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. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking BELBUCA 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 BELBUCA. They could die from taking it. Selling or giving away BELBUCA is against the law.
- Store BELBUCA securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not use BELBUCA if you have:

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

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

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- heart rhythm problems (long QT syndrome)
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of BELBUCA 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 BELBUCA. It may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking BELBUCA with certain other medicines can cause serious side effects and could lead to death.

When taking BELBUCA:

- Do not change your dose. Apply BELBUCA exactly as prescribed by your healthcare provider. Use the lowest effective dose possible for the shortest time needed.
- See the detailed Instructions for Use for information about how to apply BELBUCA.
- Do not apply BELBUCA if the package seal is broken or the film is cut, damaged, or changed in any way.
- After the film has adhered to your cheek, avoid eating or drinking until the film has completely dissolved, usually within 30 minutes.
- Avoid touching or moving the buccal film with your tongue or fingers.
- **Do not chew, swallow, snort or inject BELBUCA. This will result in uncontrolled delivery of buprenorphine and may cause you to overdose and die.**
- **Call your healthcare provider if the dose you are using does not control your pain.**
- **Do not stop using BELBUCA without talking to your healthcare provider.**
- Dispose of expired, unwanted, or unused BELBUCA by removing the BELBUCA film from the foil packaging, and promptly flushing down the toilet (if a drug takeback option is not readily available). Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While using BELBUCA DO NOT:

- Drive or operate heavy machinery, until you know how BELBUCA affects you. BELBUCA 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 BELBUCA may cause you to overdose and die.

The possible side effects of BELBUCA are:

- nausea, constipation, headache, vomiting, dizziness, and sleepiness. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help or call 911 right away 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 BELBUCA. 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: BioDelivery Sciences International, Inc., Raleigh, NC 27612,
www.BELBUCA.com or call 1-800-469-0261.

Instructions for Use

BELBUCA (bel-BUE-kuh) (buprenorphine buccal film), CIII

Before you use BELBUCA buccal film, it is important that you read the Medication Guide and these Patient Instructions for Use so that you use BELBUCA the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use BELBUCA.

Important:

- BELBUCA buccal film is sealed in a foil package. **Do not open the package until ready to use.** After opening, use the entire BELBUCA buccal film right away.
- Do not apply BELBUCA buccal film if the package seal is broken or the film is cut, damaged, or changed in any way.
- BELBUCA buccal film is available in different strengths. Make sure you have the strength that has been prescribed for you.
- Avoid placing BELBUCA buccal film to areas of the mouth with any open sores or lesions.

Open the BELBUCA package:

- Hold the foil package as shown below (see [Figure A](#)). Fold along the dotted line at the top of the foil package.



Figure A

- Keep folded and tear down or cut with scissors at the notch in the direction of the scissors on the dotted line (see [Figure B](#)). Tear all the way to the bottom. Be careful to avoid cutting and damaging the BELBUCA buccal film when using scissors.



Figure B

- Remove BELBUCA film from the foil package (see [Figure C](#)).



Figure C

Use BELBUCA buccal film as follows:

1. Use your tongue to wet the inside of your cheek or rinse your mouth with water to moisten the area in your mouth before you place BELBUCA.
2. Hold the BELBUCA buccal film with clean, dry fingers with the yellow side facing up (see [Figure D](#)).



Figure D

3. Using a finger, place the yellow side of the BELBUCA buccal film against the inside of your moistened cheek. Press and hold the BELBUCA buccal film in place for 5 seconds and then take your finger away (see **Figure E**).

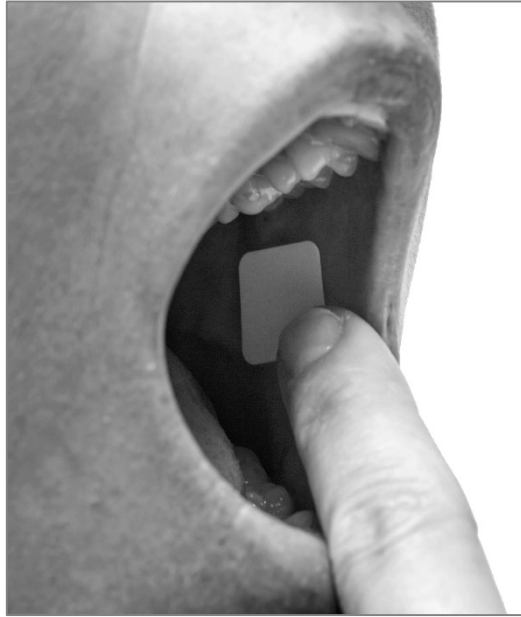


Figure E

4. The BELBUCA buccal film will stick to the inside of your cheek (see **Figure F**).



Figure F

5. Leave the BELBUCA buccal film in place until it has completely dissolved, usually within 30 minutes after you apply it.
- **Avoid eating food or drinking liquids until BELBUCA buccal film has dissolved.**
 - **Avoid touching or moving BELBUCA buccal film with your tongue or finger after it is in place.**
 - **Do not chew or swallow BELBUCA.**

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

For more information call BioDelivery Sciences International, Inc. at 1-800-469-0261.

Manufactured for:

BioDelivery Sciences International, Inc., Raleigh, NC 27612

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BEL-001-MG-Mar2021



HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SYMPROIC® (naldemedine tablets for oral use)
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

SYMPROIC is an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation (1)

DOSAGE AND ADMINISTRATION

Administration (2.1):

- Alteration of analgesic dosing regimen prior to initiating SYMPROIC is not required
- Patients receiving opioids for less than 4 weeks may be less responsive to SYMPROIC
- Discontinue SYMPROIC if treatment with the opioid pain medication is also discontinued

Dosage (2.2):

- In adults, the recommended dosage is 0.2 mg once daily with or without food

DOSAGE FORMS AND STRENGTHS

Tablets: 0.2 mg naldemedine (3)

CONTRAINDICATIONS

- Patients with known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction (4, 5.1)
- Patients with a history of a hypersensitivity reaction to naldemedine (6.1)

WARNINGS AND PRECAUTIONS

- **Gastrointestinal perforation:** Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent, or worsening abdominal pain; discontinue if development of symptoms (5.1)
- **Opioid withdrawal:** Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor symptoms of opioid withdrawal (5.2)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 2\%$) are: abdominal pain, diarrhea, nausea and gastroenteritis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioDelivery Sciences International, Inc. at 1-800-469-0261 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Strong CYP3A inducers (e.g., rifampin):** Decreased naldemedine concentrations; avoid concomitant use (7)
- **Other opioid antagonists:** Potential for additive effect and increased risk of opioid withdrawal; avoid concomitant use (7)
- **Moderate (e.g., fluconazole) and strong (e.g., itraconazole) CYP3A4 inhibitors:** Increased naldemedine concentrations; monitor for adverse reactions (7)
- **P-gp inhibitors (e.g., cyclosporine):** Monitor for adverse reactions (7)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May precipitate opioid withdrawal in a fetus (8.1)
- **Lactation:** Discontinue drug or breastfeeding taking into consideration importance of drug to mother (8.2)
- **Hepatic Impairment:** Avoid in severe impairment (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SYMPROIC is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

- Alteration of analgesic dosing regimen prior to initiating SYMPROIC is not required.
- Patients receiving opioids for less than 4 weeks may be less responsive to SYMPROIC [see *Clinical Studies (14)*].
- Discontinue SYMPROIC if treatment with the opioid pain medication is also discontinued.

2.2 Adult Dosage

The recommended dosage of SYMPROIC is 0.2 mg orally once daily with or without food.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 0.2 mg naldemedine; supplied as yellow, round, film-coated, debossed with Shionogi marking Ⓢ above the identifier code 222 on one side and 0.2 on the other side.

4 CONTRAINDICATIONS

SYMPROIC is contraindicated in:

- Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation [see *Warnings and Precautions (5.1)*].
- Patients with a history of a hypersensitivity reaction to naldemedine. Reactions have included bronchospasm and rash [see *Adverse Reactions (6.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforation

Cases of gastrointestinal perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies, or peritoneal metastases). Take into account the overall risk-benefit profile when using SYMPROIC in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue SYMPROIC in patients who develop this symptom [see *Contraindications (4)*].

5.2 Opioid Withdrawal

Clusters of symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting have occurred in patients treated with SYMPROIC [see *Adverse Reactions (6.1)*].

Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Take into account the overall risk-benefit profile when using SYMPROIC in such patients. Monitor for symptoms of opioid withdrawal in such patients.

6 ADVERSE REACTIONS

Serious and important adverse reactions described elsewhere in labeling include:

- Gastrointestinal perforation [see *Warnings and Precautions (5.1)*]
- Opioid withdrawal [see *Warnings and Precautions (5.2)*]

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to SYMPROIC in 1163 patients in clinical trials, including 487 patients with exposures greater than six months and 203 patients with exposures of 12 months.

The following safety data are derived from three double-blind, placebo-controlled trials in patients with OIC and chronic non-cancer pain: two 12-week studies (Studies 1 and 2) and one 52-week study (Study 3) [see *Clinical Studies (14)*].

In Studies 1 and 2, patients on laxatives were required to discontinue their use prior to study enrollment. All patients were restricted to bisacodyl rescue treatment during the study. In Study 3, approximately 60% of patients in both treatment groups were on a laxative regimen at baseline; patients were allowed to continue using their laxative regimen throughout the study duration. The safety profile of SYMPROIC relative to placebo was similar regardless of laxative use.

Tables 1 and 2 list common adverse reactions occurring in at least 2% of patients receiving SYMPROIC and at an incidence greater than placebo. Table 1 shows pooled 12-week data from Studies 1 and 2. Table 2 shows 12-week data from Study 3.

Table 1: Common Adverse Reactions* in Patients with OIC and Chronic Non-Cancer Pain (12-week data from Studies 1 and 2)

Adverse Reaction	SYMPROIC 0.2 mg once daily N=542	Placebo N=546
Abdominal pain**	8%	2%
Diarrhea	7%	2%
Nausea	4%	2%
Gastroenteritis	2%	1%

*Adverse reactions occurring in at least 2% of patients receiving SYMPROIC and at an incidence greater than placebo

**Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain.

Table 2: Common Adverse Reactions* in Patients with OIC and Chronic Non-Cancer Pain (12-week data from Study 3)

Adverse Reaction	SYMPROIC 0.2 mg once daily N=621	Placebo N=619
Abdominal pain**	11%	5%
Diarrhea	7%	3%
Nausea	6%	5%
Vomiting	3%	2%
Gastroenteritis	3%	1%

*Adverse reactions occurring in at least 2% of patients receiving SYMPROIC and at an incidence greater than placebo

**Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper.

Adverse reactions up to 12 months in Study 3 are similar to those listed in [Tables 1 and 2](#) (diarrhea: 11% vs. 5%, abdominal pain: 8% vs. 3%, and nausea: 8% vs. 6% for SYMPROIC and placebo, respectively).

Opioid Withdrawal

In Studies 1, 2 and 3, adverse reactions consistent with opioid withdrawal were based on investigator assessment and adjudicated based upon the occurrence of at least 3 adverse reactions potentially related to opioid withdrawal with onset of a constellation of those symptoms occurring on the same day or within one day of each other.

Adverse reactions of possible opioid withdrawal could include non-gastrointestinal (GI) symptoms (e.g., hyperhidrosis, hot flush or flushing, chills, tremor, tachycardia, anxiety, agitation, yawning, rhinorrhea, increased lacrimation, sneezing, feeling cold, and pyrexia), GI symptoms (e.g., vomiting, diarrhea, or abdominal pain), or both GI and non-GI symptoms.

In pooled Studies 1 and 2, the incidence of adverse reactions of opioid withdrawal was 1% (8/542) for SYMPROIC and 1% (3/546) for placebo. In Study 3 (52-week data), the incidence was 3% (20/621) for SYMPROIC and 1% (9/619) for placebo. Most SYMPROIC treated subjects experienced nearly equal incidence of GI only or both GI and non-GI symptoms.

Less Common Adverse Reactions:

Two patients developed symptoms of hypersensitivity following a single dose of SYMPROIC. One patient reported bronchospasm and another rash.

7 DRUG INTERACTIONS

[Table 3](#) includes drugs with clinically important drug interactions with SYMPROIC and instructions for preventing or managing the interaction.

Table 3: Clinically Relevant Interactions Affecting Naldemedine When Co-Administered with Other Drugs

Strong CYP3A Inducers (e.g., rifampin, carbamazepine, phenytoin, St. John’s Wort)	
<i>Clinical Impact</i>	Significant decrease in plasma naldemedine concentrations, which may reduce efficacy [see <i>Clinical Pharmacology (12.3)</i>]
<i>Intervention</i>	Avoid use of SYMPROIC with strong CYP3A inducers.
Other Opioid Antagonists	
<i>Clinical Impact</i>	Potential for additive effect of opioid receptor antagonism and increased risk of opioid withdrawal.
<i>Intervention</i>	Avoid use of SYMPROIC with another opioid antagonist.
Moderate (e.g., fluconazole, atazanavir, aprepitant, diltiazem, erythromycin) and Strong (e.g., itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir) CYP3A Inhibitors	
<i>Clinical Impact</i>	Increase in plasma naldemedine concentrations [see <i>Clinical Pharmacology (12.3)</i>]
<i>Intervention</i>	Monitor for potential naldemedine-related adverse reactions [see <i>Adverse Reactions (6.1)</i>].
P-glycoprotein (P-gp) Inhibitors (e.g., amiodarone, captopril, cyclosporine, quercetin, quinidine, verapamil)	
<i>Clinical Impact</i>	Increase in plasma naldemedine concentrations [see <i>Clinical Pharmacology (12.3)</i>]
<i>Intervention</i>	Monitor for potential naldemedine-related adverse reactions [see <i>Adverse Reactions (6.1)</i>].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with naldemedine in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. There is a potential for opioid withdrawal in a fetus when SYMPROIC is used in pregnant women [see *Clinical Considerations*]. SYMPROIC should be used during pregnancy only if the potential benefit justifies the potential risk.

In a rat embryo-fetal development study following oral administration of naldemedine during the period of organogenesis at doses resulting in systemic exposure approximately 23,000 times the human area under the plasma-concentration time curve (AUC) at the recommended human dose of 0.2 mg/day, no developmental abnormalities were observed. In rabbits, there were no adverse effects on embryo-fetal development following oral administration of naldemedine during the period of organogenesis at doses resulting in systemic exposure approximately 226 times the human AUC at the recommended human dose of 0.2 mg/day [see *Data*]. No effects on pre- and postnatal development were observed in rats at exposures 12 times human exposures at the recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Naldemedine crosses the placenta, and may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier.

Data

Animal Data

In rats, there were no adverse effects on embryo-fetal development following oral administration of naldemedine during the period of organogenesis at doses up to 1000 mg/kg/day (approximately 23,000 times the human exposures (AUC) at the recommended human dose). In rabbits, there were no adverse effects on embryo-fetal development following oral administration of naldemedine during the period of organogenesis at doses up to 100 mg/kg/day (approximately 226 times the human exposures (AUC) at the recommended human dose). At 400 mg/kg/day (approximately 844 times the human exposures (AUC) at the recommended human dose), effects in maternal animals included body weight loss/decreased body weight gain and food consumption, fetal loss, and premature delivery. Decreased fetal body weights at this dose may be related to the maternal toxicity observed.

In the pre- and postnatal development study, pregnant rats were administered naldemedine at oral doses up to 1000 mg/kg/day from gestation day 7 through lactation day 20. No effects on pre- and postnatal development were observed in rats at 1 mg/kg/day (approximately 12 times the human exposures (AUC) at the recommended human dose). A single dam died at parturition at 1000 mg/kg/day, and decreased body weights/body weight gain and food consumption, poor nursing, and total litter loss were noted at 30 and 1000 mg/kg/day (approximately 626 and 17,000 times the human exposures (AUC) at the recommended human dose, respectively). Decreases in the offspring viability index on Day 4 after birth were noted at 30 and 1000 mg/kg/day, and low body weights and delayed pinna unfolding in pups were noted at 1000 mg/kg/day.

8.2 Lactation

Risk Summary

There is no information regarding the presence of naldemedine in human milk, the effects on the breastfed infant, or the effects on milk production. Naldemedine was present in the milk of rats [*see Data*]. Because of the potential for serious adverse reactions, including opioid withdrawal in breastfed infants, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother. If drug is discontinued in order to minimize drug exposure to a breastfed infant, advise women that breastfeeding may be resumed 3 days after the final dose of SYMPROIC.

Data

Drug-related radioactivity was transferred into milk of lactating rats following a single oral dose of 1 mg/kg [carbonyl-¹⁴C]-naldemedine.

8.4 Pediatric Use

The safety and effectiveness of SYMPROIC have not been established in pediatric patients.

8.5 Geriatric Use

Of the 1163 patients exposed to SYMPROIC in clinical studies, 183 (16%) were 65 years of age and over, while 37 (3%) were 75 years and over. No overall differences in safety or effectiveness between these and younger patients were observed, but greater sensitivity of some older individuals cannot be ruled out. In a population pharmacokinetic analysis, no age-related alterations in the pharmacokinetics of naldemedine were observed [*see Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naldemedine has not been evaluated. Avoid use of SYMPROIC in patients with severe hepatic impairment. No dose adjustment of SYMPROIC is required in patients with mild or moderate hepatic impairment [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Single doses of naldemedine up to 100 mg (500 times the recommended dose) and multiple doses of up to 30 mg (150 times the recommended dose) for 10 days have been administered to healthy subjects in clinical studies. Dose-dependent increases in gastrointestinal-related adverse reactions, including abdominal pain, diarrhea, and nausea, were observed.

Single doses of naldemedine up to 3 mg (15 times the recommended dose) and multiple doses of 0.4 mg (twice the recommended dose) for 28 days have been administered to patients with OIC in clinical studies. Dose-dependent increases in gastrointestinal-related adverse reactions, including abdominal pain, diarrhea, nausea, and vomiting, were observed. Also, chills, hyperhidrosis, and dizziness were reported more frequently at 1 and 3 mg doses and hyperhidrosis at the 0.4 mg dose.

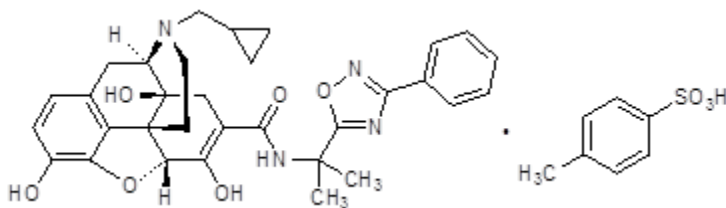
No antidote for naldemedine is known. Hemodialysis is not an effective means to remove naldemedine from the blood [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

SYMPROIC (naldemedine), an opioid antagonist, contains naldemedine tosylate as the active ingredient.

The chemical name for naldemedine tosylate is: 17-(cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxy-3,6,14-trihydroxy-N-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide 4-methylbenzenesulfonic acid.

The structural formula is:



The empirical formula for naldemedine tosylate is C₃₂H₃₄N₄O₆•C₇H₈O₃S and the molecular weight is 742.84.

Naldemedine tosylate is a white to light tan powder, soluble in dimethylsulfoxide and methanol, slightly soluble in alcohol and water, and independent of pH.

SYMPROIC (naldemedine) tablets for oral use contain 0.2 mg naldemedine (equivalent to 0.26 mg of naldemedine tosylate).

Excipients are: D-mannitol, croscarmellose sodium, magnesium stearate, hypromellose, talc, and yellow ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naldemedine is an opioid antagonist with binding affinities for mu-, delta-, and kappa-opioid receptors. Naldemedine functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids.

Naldemedine is a derivative of naltrexone to which a side chain has been added that increases the molecular weight and the polar surface area, thereby reducing its ability to cross the blood-brain barrier (BBB). Naldemedine is also a substrate of the P-glycoprotein (P-gp) efflux transporter. Based on these properties, the

CNS penetration of naldemedine is expected to be negligible at the recommended dose levels, limiting the potential for interference with centrally-mediated opioid analgesia.

12.2 Pharmacodynamics

Use of opioids induces slowing of gastrointestinal motility and transit. Antagonism of gastrointestinal mu-opioid receptors by naldemedine inhibits opioid-induced delay of gastrointestinal transit time.

Effect on Cardiac Repolarization

At a dose up to 5 times the recommended dose, SYMPROIC does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Following oral administration, naldemedine is absorbed with a time to achieve peak concentrations (T_{max}) of approximately 0.75 hours in a fasted state. Across the range of doses evaluated, the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in a dose-proportional or almost dose-proportional manner. Accumulation was minimal following multiple daily doses of naldemedine.

Food Effect

A high-fat meal decreased the rate but not the extent of naldemedine absorption. The C_{max} was decreased by approximately 35% and time to achieve C_{max} was delayed from 0.75 hours in the fasted state to 2.5 hours in the fed state, whereas there was no meaningful change in the AUC in the fed state [see *Dosage and Administration (2.2)*].

Distribution

Plasma protein binding of naldemedine in humans is 93% to 94%. The mean apparent volume of distribution during the terminal phase (V_z/F) is 155 L.

Elimination

The terminal elimination half-life of naldemedine is 11 hours.

Metabolism

Naldemedine is primarily metabolized by CYP3A to nor-naldemedine, with minor contribution from UGT1A3 to form naldemedine 3-G. Nor-naldemedine and naldemedine 3-G have been shown to have antagonistic activity for opioid receptors, with less potent effect than naldemedine.

Following oral administration of [^{14}C]-labeled naldemedine, the primary metabolite in plasma was nor-naldemedine, with a relative exposure compared to naldemedine of approximately 9% to 13%. Naldemedine 3-G was a minor metabolite in plasma, with a relative exposure to naldemedine of less than 3%.

Naldemedine also undergoes cleavage in the GI tract to form benzamidine and naldemedine carboxylic acid.

Excretion

Following oral administration of [^{14}C]-labeled naldemedine, the total amount of radioactivity excreted in the urine and feces was 57% and 35% of the administered dose of naldemedine, respectively. The amount of naldemedine excreted unchanged in the urine was approximately 16% to 18% of the administered dose. Benzamidine was the most predominant metabolite excreted in the urine and feces, representing approximately 32% and 20% of the administered dose of naldemedine, respectively. The percentage of unchanged drug in feces has not been estimated.

Use in Specific Populations

Age: Geriatric Population, Sex, Race/Ethnicity

A population pharmacokinetic analysis from clinical studies with naldemedine did not identify a clinically meaningful effect of age, sex, or race on the pharmacokinetics of naldemedine.

Renal Impairment

The pharmacokinetics of naldemedine after administration of a 0.2 mg single oral dose of SYMPROIC was studied in subjects with mild (n=8, estimated glomerular filtration rate [eGFR] of 60 to 89 mL/min/1.73 m²), moderate (n=8, eGFR 30 to 59 mL/min/1.73 m²), and severe (n=6, eGFR less than 30 mL/min/1.73 m²) renal impairment, and subjects with end-stage renal disease (ESRD) requiring hemodialysis (n=8), and compared to healthy subjects with normal renal function (n=8, estimated creatinine clearance of at least 90 mL/min). The pharmacokinetics of naldemedine between subjects in all groups were similar.

Plasma concentrations of naldemedine in subjects with ESRD requiring hemodialysis were similar when SYMPROIC was administered either pre- or post-hemodialysis, indicating that naldemedine was not removed from the blood by hemodialysis.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of a 0.2 mg single oral dose of SYMPROIC was studied in subjects with hepatic impairment classified as mild (n=8, Child-Pugh Class A) or moderate (n=8, Child-Pugh Class B) and compared with healthy subjects with normal hepatic function (n=8). The pharmacokinetics of naldemedine between subjects in all groups were similar.

The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naldemedine was not evaluated [see *Use in Specific Populations (8.6)*].

Drug Interaction Studies

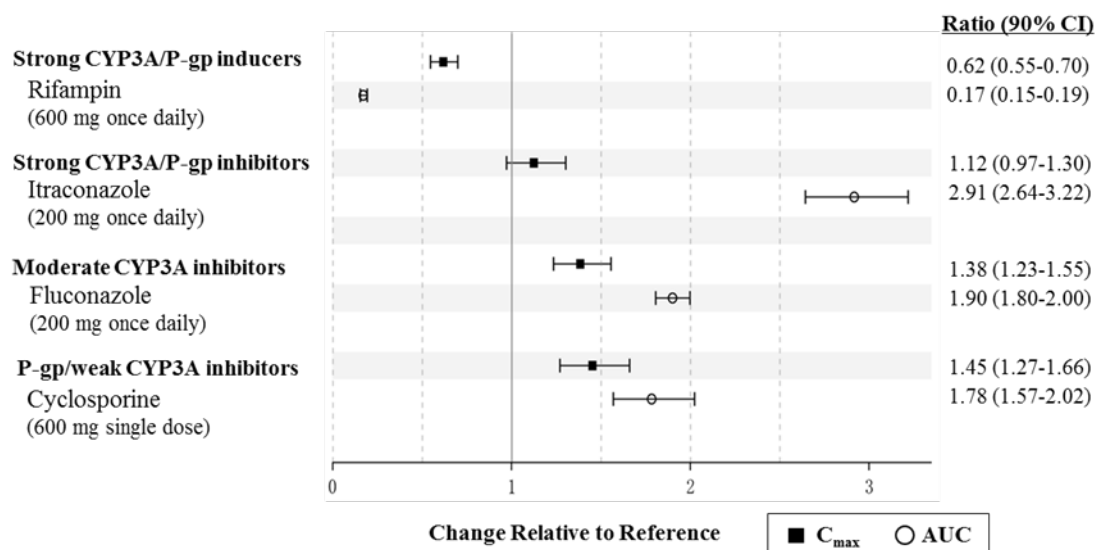
Effect of Naldemedine on Other Drugs

In *in vitro* studies at clinically relevant concentrations, naldemedine did not inhibit the major CYP enzymes (including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A11 isozymes) and is not an inhibitor of transporters (including OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, BCRP, or P-gp). Naldemedine did not cause significant induction of CYP1A2, CYP2B6, CYP3A4, UGT1A2, UGT1A6, or UGT2B7 isozymes.

Effect of Other Drugs on Naldemedine

Naldemedine is primarily metabolized by the CYP3A4 enzyme with a minor contribution from UGT1A3. Naldemedine is a substrate of P-gp. The effects of co-administered drugs on the pharmacokinetics of naldemedine are summarized in [Figure 1](#).

Figure 1: Effect of Co-Administered Drugs on the Pharmacokinetics of Naldemedine



Efavirenz (moderate CYP3A inducer): Simulation using physiologically-based pharmacokinetic modeling suggested that concomitant use of efavirenz decreases exposure to naldemedine by 43%. The clinical consequence of this decreased exposure is unknown.

No drug interaction studies have been conducted for SYMPROIC with drugs that alter gastric pH (e.g., antacids, proton-pump inhibitors).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In 2-year carcinogenicity studies, there were no drug-related neoplastic findings following oral administration of naldemedine to mice and rats at doses up to 100 mg/kg/day (approximately 17,500 and 6,300 times the human exposures (AUC) at the recommended human dose, respectively).

Mutagenesis

Naldemedine was not genotoxic in the *in vitro* bacterial reverse mutation (Ames) assay, a chromosomal aberration assay with cultured Chinese hamster lung cells, or an *in vivo* micronucleus assay with rat bone marrow cells.

Impairment of Fertility

Naldemedine was found to have no effect on fertility or reproductive performance in male and female rats at oral doses up to 1000 mg/kg/day (approximately 17,000 times the human exposures (AUC) at the recommended human dose). In female rats, prolongation of diestrous phase was noted at 10 mg/kg/day (approximately 179 times the human exposures (AUC) at the recommended human dose).

14 CLINICAL STUDIES

SYMPROIC was evaluated in two replicate, 12-week, randomized, double-blind, placebo-controlled trials (Study 1 and Study 2) in which SYMPROIC was used without laxatives in patients with OIC and chronic non-cancer pain.

Patients receiving a stable opioid morphine equivalent daily dose of at least 30 mg for at least 4 weeks before enrollment and self-reported OIC were eligible for clinical trial participation.

Patients with evidence of significant structural abnormalities of the GI tract were not enrolled in these trials.

In Studies 1 and 2, patients had to either be not using laxatives or willing to discontinue laxative use at the time of screening and willing to use only the provided rescue laxatives during the screening and treatment periods.

In Studies 1 and 2, OIC was confirmed through a two-week run in period and was defined as no more than 4 spontaneous bowel movements (SBMs) total over 14 consecutive days and less than 3 SBMs in a given week with at least 25% of the SBMs associated with one or more of the following conditions: (1) straining; (2) hard or lumpy stools; (3) having a sensation of incomplete evacuation; and (4) having a sensation of anorectal obstruction/blockage.

An SBM was defined as a bowel movement (BM) without rescue laxative taken within the past 24 hours. Patients with no BMs over the 7 consecutive days prior to and during the 2-week screening period or patients who had never taken laxatives were excluded.

In the screening and treatment periods, bisacodyl was used as rescue laxative if patients had not had a BM for 72 hours and were allowed one-time use of an enema, if after 24 hours of taking bisacodyl they still had not had a BM.

A total of 547 patients in Study 1 and 553 patients in Study 2 were randomized in a 1:1 ratio to receive SYMPROIC 0.2 mg once daily or placebo for 12 weeks. Study medication was administered without regard to meals.

The mean age of subjects in Studies 1 and 2 was 54 years; 59% were women; and 80% were white. The most common types of pain in Studies 1 and 2 were back or neck pain (61%). The mean baseline number of SBMs was 1.3 and 1.2 per week for Studies 1 and 2, respectively.

Prior to enrollment, patients were using their current opioid for a mean duration of approximately 5 years. A wide range of types of opioids were used. The mean baseline opioid morphine equivalent daily dosage was 132 mg and 121 mg per day for Studies 1 and 2, respectively.

The efficacy of SYMPROIC was assessed in Studies 1 and 2 using a responder analysis. A responder was defined as a patient who had at least 3 SBMs per week and a change from baseline of at least 1 SBM per week for at least 9 out of the 12 weeks and 3 out of the last 4 weeks in Studies 1 and 2.

The responder rates in Studies 1 and 2 are shown in [Table 4](#).

Table 4: Efficacy Responder Rates in Studies 1 and 2 in Patients with OIC and Chronic Non-Cancer Pain

	Study 1			Study 2		
	SYMPROIC 0.2 mg once daily (N=273)	Placebo (N=272)	Treatment Difference [95% CI]	SYMPROIC 0.2 mg once daily (N=276)	Placebo (N=274)	Treatment Difference [95% CI]
Responder [#]	130 (48%)	94 (35%)	13% [5%, 21%]	145 (53%)	92 (34%)	19% [11%, 27%]
p value*			0.0020			<0.0001

[#]The primary endpoint was defined as a patient who had at least 3 SBMs per week and a change from baseline of at least 1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks.

CI=Confidence Interval

*Cochran-Mantel-Haenszel test adjusted for opioid dose strata (30 to 100 mg; greater than 100 mg)

In Studies 1 and 2, the mean increase in frequency of SBMs per week from baseline to the last 2 weeks of the 12-week treatment period was 3.1 for SYMPROIC vs. 2.0 for placebo (difference 1.0, 95% CI 0.6, 1.5), and 3.3 for SYMPROIC vs. 2.1 for placebo (difference 1.2, 95% CI 0.8, 1.7), respectively.

During week 1 of the treatment period, the mean increase in frequency of SBMs per week from baseline was 3.3 for SYMPROIC vs. 1.3 for placebo (difference 2.0, 95% CI 1.5, 2.5) in Study 1 and 3.7 for SYMPROIC vs. 1.6 for placebo (difference 2.1, 95% CI 1.5, 2.6) in Study 2.

The mean increase in the frequency of complete SBM (CSBM) per week from baseline to the last 2 weeks of 12-week treatment period was 2.3 for SYMPROIC vs. 1.5 for placebo (difference 0.8, 95% CI 0.4, 1.2) in Study 1 and 2.6 for SYMPROIC vs. 1.6 for placebo (difference 1.1, 95% CI 0.6, 1.5) in Study 2. A CSBM was defined as a SBM that was associated with a sense of complete evacuation.

The change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period was 1.3 for SYMPROIC vs. 0.7 for placebo (difference 0.6, 95% CI 0.2, 0.9) in Study 1 and 1.8 for SYMPROIC vs. 1.1 for placebo (difference 0.7, 95% CI 0.3, 1.2) in Study 2.

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMPROIC is supplied as 0.2 mg naldemedine tablets as follows:

- bottle of 30 tablets - NDC 59385-041-30

Store SYMPROIC in a light resistant container at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling ([Medication Guide](#)).

Administration

Advise patients to discontinue SYMPROIC if treatment with the opioid pain medication is also discontinued.

Gastrointestinal Perforation

Advise patients to discontinue SYMPROIC and to promptly seek medical attention if they develop unusually severe, persistent or worsening abdominal pain [see *Warnings and Precautions* (5.1)].

Opioid Withdrawal

Advise patients that clusters of symptoms consistent with opioid withdrawal may occur while taking SYMPROIC and to contact their healthcare provider if these symptoms occur [see *Warnings and Precautions* (5.2)].

Pregnancy

Advise females of reproductive potential, who become pregnant or are planning to become pregnant, that the use of SYMPROIC during pregnancy may precipitate opioid withdrawal in a fetus due to the undeveloped blood-brain barrier [see *Use in Specific Populations* (8.1)].

Lactation

Advise women that breastfeeding is not recommended during treatment with SYMPROIC and for 3 days after the final dose [see *Use in Specific Populations* (8.2)].

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Manufactured for: BioDelivery Sciences International, Inc. Raleigh, NC 27612

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