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: SERIOUS LIFE-THREATENING RISKS FROM USE OF BELBUCA

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 reassess regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of BELBUCA are essential. Instruct patients on proper administration of BELBUCA to reduce the risk. (2.1, 2.8, 5.2)**
- **Accidental exposure to BELBUCA, especially in children, can result in fatal overdose of buprenorphine. (5.2)**
- **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. (5.3, 7)**
- **Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. (5.4)**
- **Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription. (5.5)**

---------- RECENT MAJOR CHANGES ----------

Boxed Warning	12/2025
Indications and Usage (1)	12/2025
Dosage and Administration (2.2, 2.3, 2.5)	12/2025
Warnings and Precautions (5.1, 5.2, 5.3, 5.12, 5.17)	12/2025

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

BELBUCA buccal film contains buprenorphine, a partial opioid agonist. BELBUCA is indicated for the management of severe and persistent pain that requires an opioid analgesic and that cannot be adequately treated with alternative options, including immediate-release opioids. (1)

Limitations of Use

- Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy, reserve opioid analgesics, including BELBUCA, for use in patients for whom alternative treatment are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1, 5.1)
- BELBUCA is not indicated as an as-needed (prn) analgesic. (1)

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

- BELBUCA should be prescribed only by healthcare professionals who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of BELBUCA for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks (2.1, 5)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse. (2.1, 5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with BELBUCA. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.2).
- Discuss opioid overdose reversal agents and options for acquiring them with the patient and/or caregiver, both when initiating and renewing treatment with BELBUCA, especially if the patient has additional risk factors for overdose, or close contacts at risk for exposure and overdose. (2.2, 5.1, 5.2, 5.3)
- BELBUCA buccal film is for oral buccal use only and is to be applied to the buccal mucosa once daily or every 12 hours. (2.1)
- Patients who are not Opioid Tolerant: 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 Opioid Analgesics 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)
- Patients with Severe Hepatic Impairment: Reduce the starting and incremental dose by half that of patients with normal liver function. (2.6, 5.19, 8.6)
- Patients with Oral Mucositis: Reduce the starting and incremental dose by half that of patients without mucositis. (2.7, 5.20)
- Periodically reassess patients receiving BELBUCA to evaluate the continued need for opioid analgesics to maintain pain control, for the signs or symptoms of adverse reactions, and for the development of addiction, abuse, or misuse. (2.4)
- Do not rapidly reduce or abruptly discontinue BELBUCA in a physically-dependent patient because rapid reduction or abrupt discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.5, 5.17)

---------- 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 ----------

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation. (5.6).
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate, particularly during initiation and titration. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Regularly evaluate 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 Collegium Pharmaceutical, Inc. at 1-855-331-5615 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Benzodiazepines: May increase buprenorphine-induced respiratory depression. Regularly evaluate 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. Evaluate patients starting CYP3A4 inhibitors or stopping CYP3A4 inducers at frequent intervals 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: Periodically assess for signs and symptoms of toxicity or overdose. (5.19, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF BELBUCA

Addiction, Abuse, and Misuse

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

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of BELBUCA, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of BELBUCA are essential. 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 Dosage and Administration (2.1, 2.8), Warnings and Precautions (5.2)]*.

Accidental Exposure

Accidental exposure of even one dose of BELBUCA, especially in children, can result in a fatal overdose of buprenorphine *[see Warnings and Precautions (5.2)]*.

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 of BELBUCA and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Neonatal Opioid Withdrawal Syndrome (NOWS)

Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription *[see Warnings and Precautions (5.5)]*.

1 INDICATIONS AND USAGE

BELBUCA is indicated for the management of severe and persistent pain that requires an opioid analgesic and that cannot be adequately treated with alternative options, including immediate-release opioids.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy *[see Warnings and Precautions (5.1)]*, reserve opioid analgesics, including 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 about the use of extended-release/long-acting opioids and how to mitigate the associated risks.
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of BELBUCA for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with BELBUCA. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5.2)]*.

- BELBUCA buccal film is for oral buccal use only and is to be applied to the buccal mucosa once daily or 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 an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient [see Warnings and Precautions (5.1, 5.2, 5.3)].

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Warnings and Precautions (5.2)]*.

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

2.3 Initial Dosage

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 an overdose. While useful tables of opioid equivalents are readily available, there is inter-patient variability in the potency of opioid drugs and opioid formulations. Frequently reevaluate patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to BELBUCA.

Use of BELBUCA in Patients who are not Opioid Tolerant

Initiate treatment in patients who are not opioid tolerant 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 patients who were not opioid tolerant 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 (5.2)]*.

Conversion from Other Opioid Analgesics to BELBUCA

- When BELBUCA therapy is initiated, discontinue all other opioid analgesics other than those used on an as needed basis for breakthrough pain when appropriate.
- 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.

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

Regular evaluation 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, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as to reassess for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1, 5.17)]*. 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 use of opioid therapy for an extended period of time, 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. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after a dosage increase), consider reducing the dosage *[see Warnings and Precautions (5)]*. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

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 (5.15), Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*. If pain is not adequately managed on BELBUCA 900 mcg, consider an alternate analgesic.

2.5 Safe Reduction or Discontinuation of BELBUCA

Do not rapidly reduce or abruptly discontinue BELBUCA in patients who may be physically dependent on opioids. Rapid reduction or abrupt discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid reduction or abrupt 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 total daily dose of opioid (including 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, evaluate 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 an extended period of time 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 (5.17), 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 (5.19), 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 (5.20), 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.

Advise patients to do the following after the product has completely dissolved in the oral mucosa: take a sip of water, swish gently around the teeth and gums, and swallow. Advise patients to wait for at least one hour after taking BELBUCA before brushing teeth *[see Warnings and Precautions (5.14), Adverse Reactions (6.2)]*.

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.

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 (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.12)]*
- Hypersensitivity (e.g., anaphylaxis) to buprenorphine *[see Warnings and Precautions (5.16), 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. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use *[see Adverse Reactions (6.2)]*.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing BELBUCA and reassess 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 frequent reevaluation for signs of addiction, abuse, or misuse. Consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

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

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. 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 careful storage of the drug during the course of treatment and the proper disposal of unused drug. 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 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 overdose reversal agents, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) 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.

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.

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 an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.1, 5.3)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3), Overdosage (10)]*.

5.3 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of BELBUCA with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids). 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. Inform patients and caregivers of this potential interaction and educate them on signs and symptoms of respiratory depression (including sedation).

If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)]*. 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)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

Use of BELBUCA for an extended period of time 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 an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1)]*.

5.5 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.

5.6 Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect *[see Dependence (9.3)]*. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) *[see Dosage and Administration (2.5), Warnings and Precautions (5.17)]*.

5.7 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 (5.2)]*.

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 *[see Warnings and Precautions (5.2)]*.

Regularly evaluate patients, particularly when initiating and titrating BELBUCA and when BELBUCA is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2, 5.3), Drug Interactions (7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 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.

5.9 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)]*. Regularly evaluate 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 CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), BELBUCA may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with BELBUCA.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of BELBUCA in patients with impaired consciousness or coma.

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 postmarketing adverse event 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 periodically reassess during treatment with BELBUCA.

5.12 Risk of Gastrointestinal Complications

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. Regularly evaluate patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain) and, if necessary, adjust opioid therapy as clinically

appropriate *[see Clinical Pharmacology (12.2)*.

5.13 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. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during BELBUCA therapy.

5.14 Dental Adverse Events

Cases of dental caries, some severe (i.e., tooth fracture, tooth loss), have been reported following the use of transmucosal buprenorphine-containing products. Reported events include cavities, tooth decay, dental abscesses/infection, rampant caries, tooth erosion, fillings falling out, and, in some cases, total tooth loss. Treatment for these events included tooth extraction, root canal, dental surgery, as well as other restorative procedures (i.e., fillings, crowns, implants, dentures). Multiple cases were reported in individuals without any prior history of dental problems.

Refer patients to dental care services and encourage them to have regular dental checkups while taking BELBUCA. Educate patients to seek dental care and strategies to maintain or improve oral health while being treated with transmucosal buprenorphine-containing products. Strategies include, but are not limited to, gently rinsing the teeth and gums with water and then swallowing after BELBUCA has been completely dissolved in the oral mucosa. Advise patients to wait for at least one hour after taking BELBUCA before brushing teeth *[see Dosing and Administration (2.8)]*.

5.15 QTc Prolongation

Thorough QT studies with buprenorphine products have demonstrated QT prolongation ≤15 msec. This QTc prolongation effect does not appear to be mediated by hERG channels. Based on these two findings, buprenorphine is unlikely to be pro-arrhythmic when used alone in patients without risk factors. The risk of combining buprenorphine with other QT-prolonging agents is not known.

Consider these observations in clinical decisions when prescribing BELBUCA to patients with risk factors such as hypokalemia, bradycardia, recent conversion from atrial fibrillation, congestive heart failure, digitalis therapy, baseline QT prolongation, subclinical long-QT syndrome, or severe hypomagnesemia *[see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*.

5.16 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.

5.17 Withdrawal

Do not rapidly reduce or 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.

5.18 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.

5.19 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 periodically assessed 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)]*.

5.20 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. Regularly evaluate these patients for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3)]*.

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 (5.2)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.6)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.8)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Hepatotoxicity *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- QTc Prolongation *[see Warnings and Precautions (5.15)]*
- Anaphylactic/Allergic Reactions *[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 ≤ 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 (≥ 2%) leading to discontinuation were nausea, vomiting, and liver function test abnormality.

The most common adverse events (≥ 5%) reported by patients who were not opioid tolerant, opioid-experienced patients, 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 ≥ 5% of Patients during the Open-Label Titration Phase and Double-Blind Treatment Phase of Controlled Studies: Opioid-Naïve Patients Who Were Not Opioid Tolerant

	Open-Label Titration Phase	Double-Blind Treatment Phase	
MedDRA Preferred Term	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 ≥ 5% of Patients during the Open-Label Titration Phase and Double-Blind Treatment Phase of Controlled Studies: Opioid-Experienced Patients

	Open-Label Titration Phase	Double-Blind Treatment Phase	
MedDRA Preferred Term	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%
Dizziness	5%	2%	<1%
Somnolence	5%	1%	<1%
Drug Withdrawal Syndrome	0%	4%	10%

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

	Open-Label Titration Phase	Double-Blind Treatment Phase	
MedDRA Preferred Term	**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 (≥ 5%), common (≥ 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 (≥ 5%): nausea, constipation, headache, vomiting, fatigue, dizziness, and somnolence.

Common (≥ 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 use of opioids for an extended period of time. *[see Clinical Pharmacology (12.2)]*.

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see Warnings and Precautions (5.6)]*.

Local reactions: dental decay (including caries, tooth fracture, and tooth loss).

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids, and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term *[see Warnings and Precautions (5.12)]*.

Adverse Reactions from Observational Studies

A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either: 1) filled multiple extended-release/long-acting opioid analgesic prescriptions during a 90-day period (n=978); or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months.

Over 12 months:

- approximately 1% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and
- approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse *[defined in Drug Abuse and Dependence (9.2)]*, respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid-involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. *New long-term use* was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with BELBUCA.

Table 5: Clinically Significant Drug Interactions

Benzodiazepines	
Clinical Impact:	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.
Intervention:	Regularly evaluate 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	
Clinical Impact:	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 *[see Warnings and Precautions (5.3)]*.

Intervention:	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. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2, 5.3)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), and other opioids, alcohol.
Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of BELBUCA 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 Clinical Pharmacology (12.3)]*, potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to buprenorphine.
Intervention:	If concomitant use is necessary, consider dosage reduction of BELBUCA until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation. If a CYP3A4 inhibitor is discontinued, consider increasing the BELBUCA dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of BELBUCA and CYP3A4 inducers can decrease the plasma concentration of buprenorphine *[see Clinical Pharmacology (12.3)]*, 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 Clinical Pharmacology (12.3)]*, which could increase or prolong both therapeutic effects and adverse reactions and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the BELBUCA dosage until stable drug effects are achieved. Evaluate patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider BELBUCA dosage reduction and evaluate patients at frequent intervals for signs of respiratory depression and sedation.
Examples:	Rifampin, carbamazepine, phenytoin
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue BELBUCA if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2)]*.
Intervention:	The use of BELBUCA is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of BELBUCA and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine
Muscle Relaxants	
Clinical Impact:	Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Because respiratory depression may be greater than otherwise expected, 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 consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.3)]*.
Examples:	cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Evaluate patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Evaluate patients for signs of urinary retention or reduced gastric motility when BELBUCA is used concomitantly with anticholinergic drugs.
Antiretrovirals: Nucleoside reverse transcriptase inhibitors (NRTIs)	
Clinical Impact:	Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected.
Intervention:	None
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Clinical Impact:	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.
Intervention:	If prescribing an NNRTI to a patient taking BELBUCA frequently reevaluate for this interaction and adjust dosing as necessary.
Examples:	efavirenz, nevirapine, etravirine, delavirdine
Antiretrovirals: Protease inhibitors (PIs)	
Clinical Impact:	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.
Intervention:	Evaluate patients taking BELBUCA and atazanavir with and without ritonavir and reduce the dose of BELBUCA if warranted.
Examples:	atazanavir, ritonavir

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time 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 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 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Use of opioid analgesics for an extended period of time 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 overdose reversal agent, such as naloxone or nalmefene, 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

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), 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.

Respiratory depression is the chief risk for elderly patients treated with opioids and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of BELBUCA slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.7), 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 regularly evaluate 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)]*. Regularly evaluate 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, regularly evaluate 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 (5.19), 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 high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of BELBUCA increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of BELBUCA with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of BELBUCA abuse include those with a history of prolonged use of any opioid, including products containing buprenorphine, those with a history of drug or alcohol abuse, or those who use BELBUCA in combination with other abused drugs.

"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 provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

BELBUCA, like other opioids, can be diverted for nonmedical 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 reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of BELBUCA

Abuse of BELBUCA poses a risk of overdose and death. This risk is increased with concurrent use of BELBUCA with alcohol and/or other substances, including other opioids and benzodiazepines *[see Warnings and Precautions (5.1, 5.3), Drug Interactions (7)]*.

BELBUCA is approved for buccal use only. 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 chewing, 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 use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Do not rapidly reduce or 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 an extended period of time 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 (5.17)]*.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with buprenorphine 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, hypoglycemia, 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)]*. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

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 measures.

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.

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.

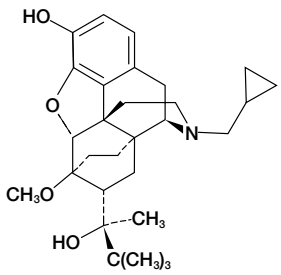
In an individual physically dependent on opioids, administration of an opioid overdose reversal agent may precipitate an acute withdrawal. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the reversal agent administered. If a decision is made to treat serious respiratory

depression in the physically dependent patient, administration of the reversal agent should be initiated with care and by titration with smaller than usual doses of the reversal agent.

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, [5α, 7α, (S)]. Its structural formula is as follows:



.HCl

The molecular weight of buprenorphine hydrochloride is 504.10; the empirical formula is $C_{29}H_{41}NO_4$·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, transient elevations in serum amylase, and opioid-induced esophageal dysfunction (OIED).

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.

Use of opioids for an extended period of time 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 opioid agonists. 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 (± SD) BELBUCA Pharmacokinetic Parameters

Regimen	Dosage (mcg)	C_{max} (ng/mL)	AUC_{0-t} (h·ng/mL)	$AUC_{0-\infty}$ (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}, $AUC_{0\text{-last}}$, 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}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were increased (Table 8) *[see Dosage and Administration (2.6), Warnings and Precautions (5.19), 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%
	$AUC_{0\text{-last}}$	64%
	Half-life	35%
Severe	C_{max}	72%
	$AUC_{0\text{-last}}$	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 (5.20)]*.

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/m^2 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 [^{3}H]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 patients who were not opioid tolerant 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 Patients who were not Opioid Tolerant 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.

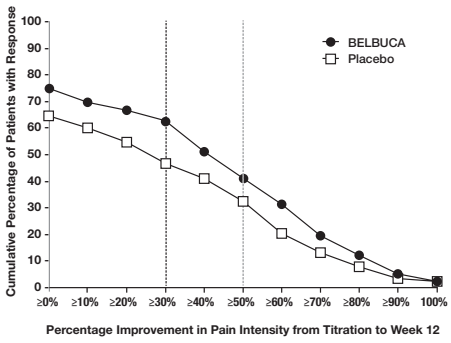
During the first 2 weeks of double-blind treatment, patients were allowed up to 2 tablets per day of hydrocodone/acetaminophen 5/325 mg as supplemental analgesia to minimize opioid withdrawal symptoms in patients randomized to placebo. Thereafter, the supplemental analgesia was limited to 1 to 2 tablets 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.

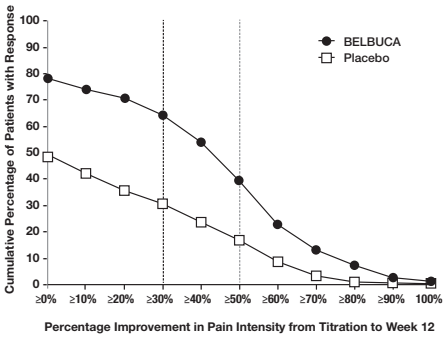
During the double-blind period, patients were permitted to take up to 2 doses of 5/325 mg or 10/650 mg of hydrocodone/acetaminophen per day for the first 2 weeks to minimize opioid withdrawal symptoms in patients randomized to placebo. After the first 2 weeks, patients were permitted to take 1 dose of 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.

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. Inform patients that leaving BELBUCA unsecured can pose a deadly risk to others in the home *[see Warnings and Precautions (5.1, 5.2), Drug Abuse and Dependence (9.2)]*.

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 (5.2)]*.

Accidental Exposure

Inform patients that accidental exposure, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*.

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 (e.g., non-benzodiazepine sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids), and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.3), Drug Interactions (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)]*.

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Discuss with the patient the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, 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 effects of opioid overdose reversal agents like naloxone and nalmefene 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 an opioid overdose reversal agent is administered [see Overdosage (10)].

Advise patients and caregivers:

- how to treat with the overdose reversal agent in the event of an opioid overdose.
- to tell family and friends about their overdose reversal agent 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 overdose reversal agent. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.6), Adverse Reactions (6.2)]*.

Serotonin Syndrome

Inform patients that BELBUCA could cause a rare but potentially life-threatening condition called serotonin syndrome 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)]*.

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.
- Advise patients that, after BELBUCA has completely dissolved in the oral mucosa, to take a sip of water, swish it gently around their teeth and gums, and swallow. Advise patients to wait for at least one hour after taking BELBUCA before brushing teeth *[see Warnings and Precautions (5.14)]*.
- 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.
- Refer patients to dental care services and encourage them to have regular dental checkups while taking BELBUCA. Instruct patients to inform their dentist that they have started therapy on BELBUCA *[see Warnings and Precautions (5.14)]*.

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)]*.

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)]*.

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)]*.

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 (5.8)]*.

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 (5.16)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of BELBUCA for an extended period of time 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

Inform female patients of reproductive potential 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)]*.

Healthcare professionals can telephone Collegium Pharmaceutical, Inc. at 1-855-331-5615 or access www.BELBUCA.com for information on this product.

Distributed by:
Collegium Pharmaceutical, Inc.
Stoughton, MA 02072 USA

BEL-002-PI-Dec2025

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 severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine when other pain 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 to be taken on an "as needed" basis.

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. Ask your healthcare provider about medicines like naloxone or nalmefene that can be used in an emergency to reverse an opioid overdose.
- Taking BELBUCA with other opioid medicines, benzodiazepines, gabapentinioids (gabapentin or pregabalin), 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
- tooth problems, including a history of cavities.
- 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:

- **noticing your pain getting worse.** If your pain gets worse after you take BELBUCA, do not take more of BELBUCA without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking BELBUCA.
- **pregnant or planning to become pregnant.** Use of BELBUCA for an extended period of time 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.
- After BELBUCA is completely dissolved, rinse your mouth with water and swallow. Wait for at least one hour before brushing teeth.
- Report any problems with your teeth immediately to your healthcare provider and schedule an appointment with a dentist. Tell your dentist that you have started taking BELBUCA. 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 healthcare provider 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: Collegium Pharmaceutical, Inc., Stoughton, MA 02072, www.BELBUCA.com or call 855-331-5615

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised Dec2025

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)**.

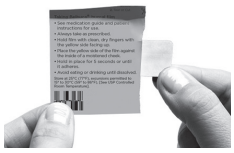


Figure C

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).**

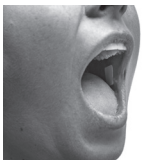


Figure F

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.**
- After BELBUCA is completely dissolved, rinse your mouth with water and swallow. Wait at least one hour before brushing your teeth.

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

For more information call Collegium Pharmaceutical, Inc. at 855-331-5615.

Manufactured for:
Collegium Pharmaceutical, Inc., Stoughton, MA 02072

BEL-001-MG-Dec 2025

Collegium PHARMACEUTICAL