INDICATION

*BELBUCA® (buprenorphine buccal film) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with long-acting opioid formulations, reserve BELBUCA for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- BELBUCA is not indicated as an as-needed (prn) analgesic.

Please see Important Safety Information and full Prescribing Information, including Boxed Warning on Addiction, Abuse, and Misuse and other serious risks accompanying this piece, or at belbuca.com/PI.

IMPORTANT SAFETY INFORMATION about BELBUCA®

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

Addiction, Abuse, and Misuse

BELBUCA exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing BELBUCA, and monitor regularly for these behaviors and conditions.

Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the FDA has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression

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

Accidental Exposure

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of BELBUCA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risks from Concomitant Use with Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

50.2 MILLION
AMERICANS SUFFER
from chronic pain[1]

153 MILLION
OPIOID PRESCRIPTIONS
dispensed in 2019[2]

9.2 MILLION
ADULTS MISUSED
prescription analgesics[3]

For your pain patients, prescription opioids can be an important option but may lead to addiction, abuse, or misuse and can cause serious side effects, such as life-threatening or fatal respiratory depression.

When other pain therapies are inadequate for your patients and you have made the decision to prescribe an opioid, we offer a portfolio of treatment options that represent a step forward in responsible pain management.

Collegium® PHARMACEUTICAL

BELBUCA®: Buprenorphine, a Schedule III opioid for chronic pain*

Buprenorphine:

- Is a partial agonist at the mu-opioid receptor[4,5]
- Is an antagonist at the kappa-opioid receptor[4,5,6]
- Binds with high affinity and detaches slowly from mu-opioid receptors[4,6,7]
- Appears to exhibit a dose-ceiling effect[4]

There is NO associated MME conversion factor with BELBUCA.[8]

- If your state PDMP requires an associated morphine milligram equivalent (MME) conversion factor, please use the 2016 conversion factors

The MME conversion factors were removed by the Centers for Disease Control and Prevention (CDC) in its September 2017 revision.

Scan to view the CDC summary information on opioids and their oral MME conversion factor.

Buprenorphine is a Schedule III drug[9]

SCHEDULE I[10]

Schedule I substances have no currently accepted use in the United States. They have a lack of accepted safety for use under medical supervision and a high potential for abuse.

SCHEDULE II[10]

Schedule II substances have a high potential for abuse, with use potentially leading to severe psychological or physical dependence.

SCHEDULE III[10]

Schedule III substances have a potential for abuse less than Schedule I or II substances but more than Schedule IV, and abuse may lead to moderate or low physical and psychological dependence.

SCHEDULE IV[10]

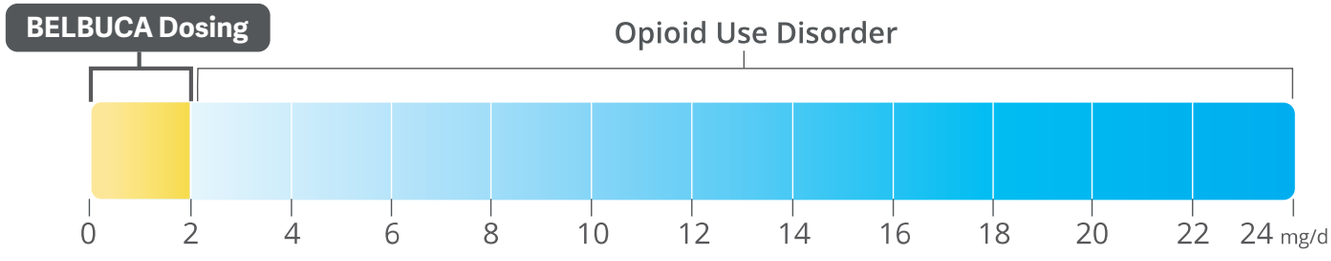
Schedule IV substances have a low potential for abuse and a low risk for dependence.

SCHEDULE V[10]

Schedule V substances have a low potential for abuse compared with Schedule IV substances and consist primarily of preparations containing limited quantities of certain narcotics.

Clinical studies have demonstrated that:

- Lower doses of buprenorphine are effective for treating chronic pain: 75 mcg (0.075 mg) up to 1800 mcg (1.8 mg)[4,11]
- Higher doses are used to treat patients with opioid use disorder: 2 mg up to 24 mg[6,11]



IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

BELBUCA is contraindicated in patients with significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; known or suspected gastrointestinal obstruction, including paralytic ileus; and hypersensitivity (e.g., anaphylaxis) to buprenorphine.

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BELBUCA®
(buprenorphine buccal film)
75 • 150 • 300 • 450 • 600 • 750 • 900 mcg
Rethink Relief

BELBUCA® is the first and only Schedule III long-acting opioid to use buccal film technology[4,5,9,12]

The BEMA® Technology Advantage: Enhanced Bioavailability

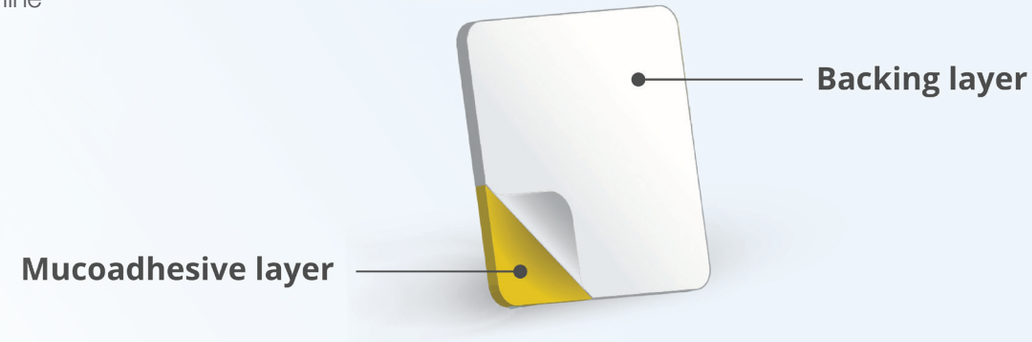
The buccal film technology allows for 46% to 65% bioavailability of buprenorphine[13,14]

Mucoadhesive layer[4]

- Contains a dose of buprenorphine
- Adheres within seconds upon contact with the inside of cheek
- Stays in place once adhered (no need to continue holding)

Backing layer[4]

- Creates a barrier that helps facilitate one-way flow of medication[4,5]
- Directs buprenorphine to the buccal mucosa
- Reduces the chance of buprenorphine flowing back into the mouth where it might be swallowed



For illustrative purposes only.
Not the actual product or size.

BEMA technology advantages[5,14]

- Bypasses first-pass metabolism in the gastrointestinal tract
- Releases buprenorphine rapidly into the bloodstream, with peak plasma concentration within 3 hours
- BELBUCA exhibits a mean plasma elimination half-life of 27.6±11.2 hours

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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

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BELBUCA® was studied in patients previously taking common CII opioids

The safety and efficacy of BELBUCA was evaluated in a multicenter, double-blind, placebo-controlled study in opioid-experienced patients with moderate to severe chronic low back pain.[15]

Opioid Medications Used in ≥5% of Patients at Screening*: N=810[16]

Hydrocodone† (n=461)	Tramadol (n=274)	Oxycodone† (n=150)	Morphine (n=41)
57%	34%	19%	5%

*Patients may have been taking multiple short- and/or long-acting formulations of opioid medication(s).
†Patients on hydrocodone or oxycodone may have been taking single- or combination-agent formulation(s).

Potential limitations of short-acting opioids (SAOs) when treating chronic pain

- Provide short-term pain relief[18]
- Multiple daily doses required to achieve around-the-clock relief[18]
- Individual's tolerability of current treatment[19]
- Nighttime awakenings due to pain[18]

83% **of patients reported poorly controlled pain on their current opioid medications at screening (randomized patients)[17]**

What are reasons to transition patients in your practice beyond short-acting opioids (SAOs)?

IMPORTANT SAFETY INFORMATION

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

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of BELBUCA with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. Follow patients closely for signs and symptoms of respiratory depression and sedation.

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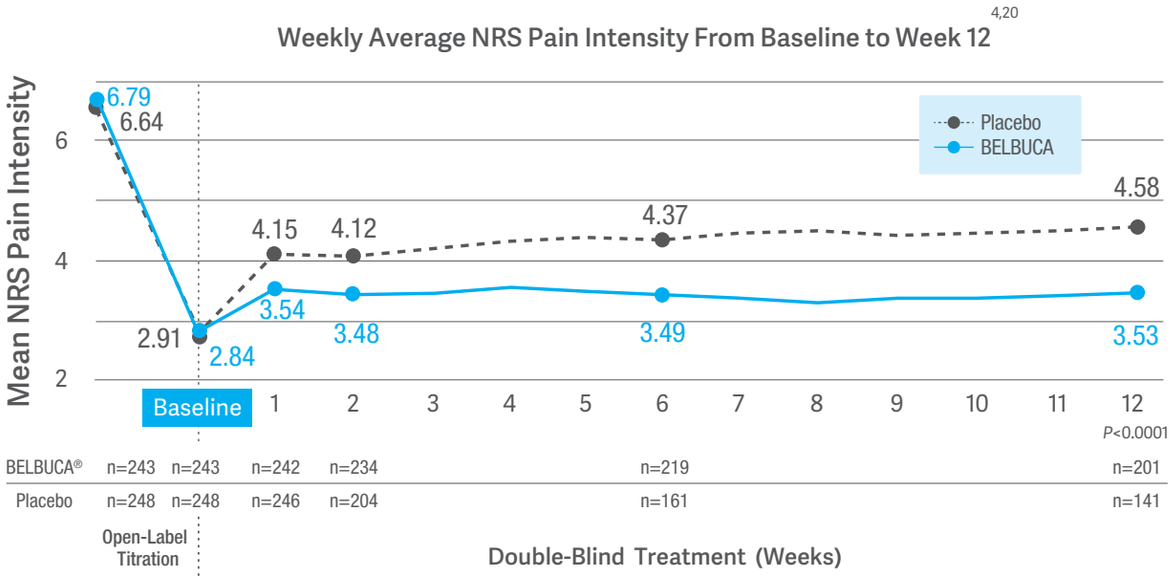
Patients experienced significant and sustained pain relief with BELBUCA®

Patients Experienced Significant Reduction in Pain Through Week 12[4,20]

- Opioid-experienced patients reported a significant reduction in mean numerical rating scale (NRS) pain intensity scores where 0=*no pain* and 10=*worst pain imaginable*
- Consistent levels of chronic pain relief were maintained in patients after titrating to an optimal dose



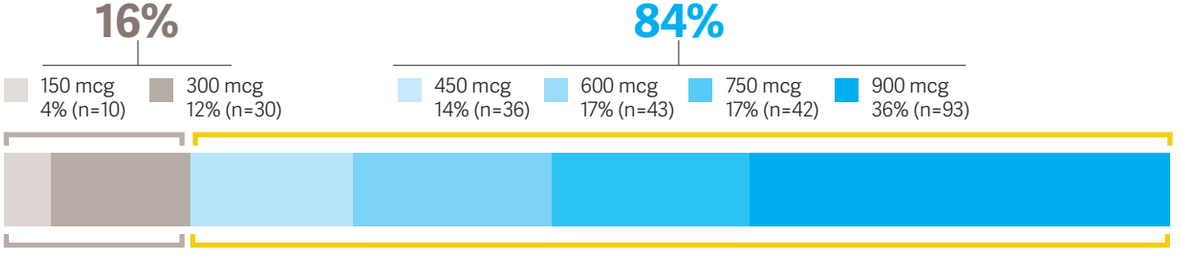
NRS=numeric rating scale, where 0=*no pain* and 10=*worst pain imaginable*.

During open label titration, the dose of BELBUCA was titrated every 4 to 8 days until patients reached their optimal, lowest effective dose, on average, in **24.5 days.**[15,21,22]

Optimal dose was defined as[22]:

- A dose satisfactory for both analgesia and tolerability (preferably without the need for rescue medication)
- No more than 1 dose of hydrocodone/acetaminophen (HC/APAP) 5/325 mg/d (1 or 2 tablets per dose)
- Patients were willing to continue at the same dose until end of study

84% of patients reached optimal dose at doses ≥450 mcg q12h[15]



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IMPORTANT SAFETY INFORMATION

Addiction, Abuse, and Misuse

- BELBUCA contains buprenorphine, a Schedule III controlled substance. As an opioid, BELBUCA exposes users to the risks of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BELBUCA. Addiction can occur at recommended dosages and if the drug is misused or abused.

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Tolerability profile with BELBUCA® in opioid-experienced patients comparable to placebo

- Most common adverse events (≥5% of patients) were nausea, constipation, vomiting, headache, dizziness, and somnolence[4]
- Discontinuation due to adverse events[4]:
  - 10% (81 of 810 patients) during the open-label titration phase
  - 2% during the double-blind treatment phase, vs 5% of patients in the placebo group
- Discontinuation due to nausea in patients taking BELBUCA was[23]:
  - 2.6% (21 of 810 patients) during the open-label titration phase
  - 0.4% (1 of 254 patients) during the double-blind treatment phase
- There were no reports of respiratory depression in the pivotal phase III clinical studies of BELBUCA, including the long-term safety study[13,15]

Adverse Events Reported in ≥5% of Patients[4]

	Open-Label Titration Phase	Double-Blind Treatment	
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%

Study Design: The efficacy and safety of BELBUCA was evaluated in a multicenter, double-blind, placebo-controlled study in opioid-experienced patients with moderate to severe chronic low back pain. The primary objective of this study was to determine the change in mean average NRS daily pain intensity score from baseline to week 12 of the double-blind treatment period. In all, 810 patients were dosed in the open-label titration phase of the study. Of those, 511 (63%) were able to titrate to an optimal dose by the end of the open-label titration phase. Double-blind study medication was given to 511 patients, with 254 randomized to BELBUCA and 257 to placebo. In all, 206 (81%) patients who received BELBUCA and 147 (57%) who received placebo completed the 12-week treatment phase. Patients were permitted to take HC/APAP 5/325 mg (1 tablet) every 6 hours as needed for analgesic rescue, up to a maximum of 4 doses per day during the opioid-taper phase. When patients received ≤30 mg MME for at least 3 days, they were eligible to enter the open-label dose-titration period, where they were permitted to take rescue medication up to 4 doses (1 or 2 tablets) of HC/APAP 5/325 mg/d. During the 12-week treatment phase, patients in both the BELBUCA and placebo groups were allowed rescue medication up to 2 doses (1 or 2 tablets) of 5/325 mg/d of HC/APAP for the first 2 weeks and allowed 1 dose (1 or 2 tablets) of 5/325 mg/d thereafter.[4,15]

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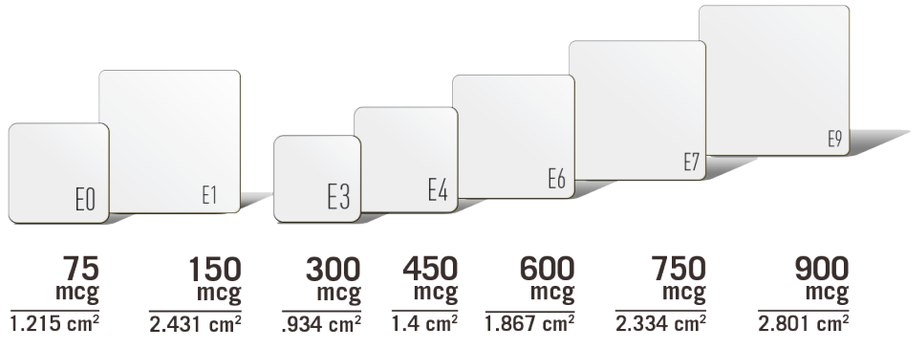
Targeting a maintenance dose

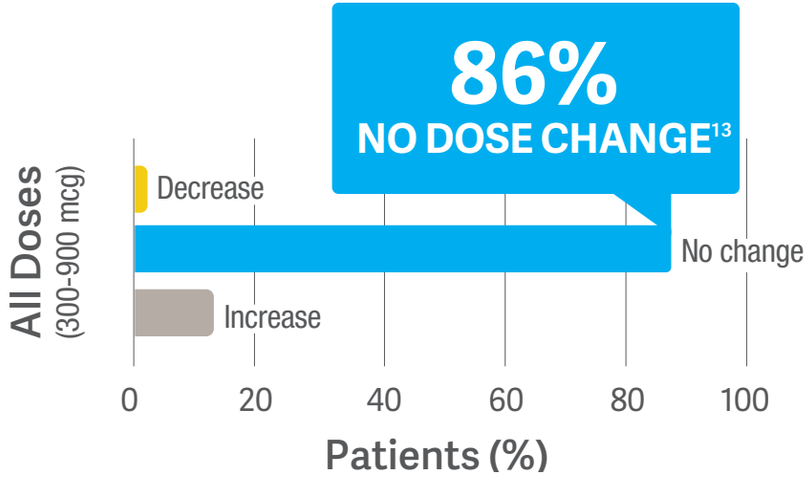
Seven strengths to identify optimal dose[4]

Individualize treatment with 7 dose strengths and titrate to the lowest effective dose that provides minimal adverse events (AEs).



In a separate 48-week, long-term safety study majority of patients (86.2%) were maintained at their optimal dose with no changes[13]*

- 88% of patients reached an optimal dose of ≥450 mcg
- Need for rescue medication decreased from 3 tablets per day to 1.1 tablets per day on average
- The most commonly reported AEs in the long-term treatment phase included vomiting (5.1%), upper respiratory infections (4.8%), back pain (3.7%), diarrhea (3.4%), nasopharyngitis (3.2%), urinary tract infection (3.0%), and falls (3.0%)
- There were no reports of respiratory depression in the phase III, long-term safety study



*The long-term safety, tolerability, and analgesic efficacy of BELBUCA was evaluated in an open-label, single-arm study in opioid-naive and opioid-experienced patients with moderate to severe chronic pain. The primary objective was to determine long-term safety and tolerability of BELBUCA. The open-label titration phase of the study included 506 patients; 435 entered the long-term treatment phase. Of those, 158 patients (36.3%) completed the long-term treatment phase. The majority of patients discontinued long-term treatment due to the sponsor's decision to terminate the study (n=141; 32.4%). Other reasons for study discontinuation included withdrawal by the patient (n=36; 8.3%), lost to follow-up (n=21; 4.8%), adverse events (n=17; 3.9%), protocol violation (n=12; 2.8%), and lack of efficacy (n=8; 1.8%).[13]

The study demonstrated the ability to safely and effectively titrate to an optimal dose of BELBUCA and maintain that dose for up to 48 weeks in both opioid-naive and opioid-experienced patients.[13]

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IMPORTANT SAFETY INFORMATION

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

- The use of BELBUCA in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.
- BELBUCA-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of BELBUCA.
- Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared with younger, healthier patients.

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Starting your patients on BELBUCA®[4]

When transitioning opioid-experienced patients, start by tapering their current opioid dose to no more than 30 mg oral MME daily

Scan to use the MME Conversion Calculator tool to determine the appropriate buprenorphine dose.

Determine the appropriate BELBUCA starting dose based on the patient's total daily opioid dose prior to taper

Step 1	Step 2	Step 3					
FIND PREVIOUS DAILY DOSE (PRIOR TO TAPER)	**DETERMINE BELBUCA STARTING DOSE**	**TITRATE BELBUCA TO OPTIMAL DOSE***					
		1	2	3	4	5	6
<30 mg oral MME	75 mcg† QD or q12h	150 mcg	300 mcg	450 mcg	600 mcg	750 mcg	900 mcg
30–89 mg oral MME	150 mcg q12h	300 mcg	450 mcg	600 mcg	750 mcg	900 mcg	
90–160 mg oral MME	300 mcg q12h	450 mcg	600 mcg	750 mcg	900 mcg		

- For patients previously taking oral MME >160 mg, consider an alternate analgesic

*Titration should occur no more frequently than every 4 days, with doses delivered in q12h intervals.
†Opioid-naive and opioid-intolerant patients: Begin at 75 mcg QD or q12h for at least 4 days; increase to 150 mcg q12h before continuing to titrate in increments of 150 mcg q12h.

NOTE: Only doses up to 450 mcg q12h were studied in opioid-naive patients.
Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and after dosage increases with BELBUCA, and adjust the dosage accordingly. Close monitoring is of particular importance when converting from methadone to other opioid agonists, including BELBUCA. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

How are you currently transitioning patients from one opioid therapy to another?

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Post hoc analyses combined data for patients from opioid-experienced and opioid-naive clinical trials[15,24,25]

Pain relief in moderate and severe chronic pain patients

In the table (right), ALL patients were receiving BELBUCA® as randomization had not yet occurred.

Pain scores were evaluated **before titration** (before receiving unblinded BELBUCA). Patients were then titrated to an optimal dose of BELBUCA. Pain scores were reevaluated **before randomization** (before starting double-blind treatment).

Once optimal dose was achieved, eligible patients were randomly assigned (1:1 ratio) to continue BELBUCA or transition to placebo.

Study Design: Post hoc analyses combined data for patients from opioid-experienced and opioid-naive clinical trials and evaluated the mean difference in average daily NRS pain score from baseline (the start of double-blind treatment). Across both the opioid-naive and opioid-experienced clinical trials, 971 patients were randomly assigned to buprenorphine buccal film or placebo. Patients were stratified by average pain severity in the 7 days before the start of open-label titration with mild pain defined as ≤4, moderate pain as an average of 5 or 6, and severe pain as an average ≥7 on the NRS pain scale.[25]

Moderate
20%
(196/971*) of patients reported experiencing moderate pain[15,24]

Severe
76%
(737/971*) of patients reported experiencing severe pain[15,24]

Characteristic	Pain Severity			
	Moderate (NRS 5-6)		Severe (NRS 7-10)	
	BBF	PBO	BBF	PBO
n	102	94	366	371
Average pain score before titration mean (SD)	5.6 (0.4)	5.5 (0.3)	7.5 (0.8)	7.5 (0.8)
Average pain score before randomization mean (SD)	2.6 (0.9)	2.7 (0.8)	3.0 (1.0)	2.9 (1.1)

*A subset of patients are not shown in the table above.

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IMPORTANT SAFETY INFORMATION

Risk of Overdose in Patients With Moderate or Severe Hepatic Impairment

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

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Transition From SAOs
Sam

Age: 34

Occupation: Retail employee

Medical history: Chronic low back pain since her second pregnancy, diabetes

Patient concerns: Frequent need for short-acting opioids during working hours when her back pain is aggravated. Needs to take other daily medications for other conditions. Frustrated that she must watch the clock to time her pain medications.

Patients like Sam may be appropriate candidates for BELBUCA.

Buprenorphine Patch Failure
Brett

Age: 45

Occupation: EMT

Medical history: Chronic low back pain due to the manual demands of his job

Patient concerns: Not achieving optimal pain relief on his current adhesive patch therapy, and experiences skin irritation at the patch site.

Patients like Brett may be appropriate candidates for BELBUCA.

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INDICATION

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Limitations of Use

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- **complete a REMS-compliant education program,**
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- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

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

Accidental Exposure

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of BELBUCA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risks from Concomitant Use with Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

CONTRAINDICATIONS

BELBUCA is contraindicated in patients with significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; known or suspected gastrointestinal obstruction, including paralytic ileus; and hypersensitivity (e.g., anaphylaxis) to buprenorphine.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

- BELBUCA contains buprenorphine, a Schedule III controlled substance. As an opioid, BELBUCA exposes users to the risks of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BELBUCA. Addiction can occur at recommended dosages and if the drug is misused or abused.
- Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing BELBUCA and monitor all patients receiving BELBUCA for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as BELBUCA, but use in such patients necessitates intensive counseling about the risks and proper use of BELBUCA, along with intensive monitoring for signs of addiction, abuse, or misuse.
- Consider prescribing naloxone for the emergency treatment of opioid overdose.
- Abuse or misuse of BELBUCA by swallowing may cause choking, overdose, and death.
- Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing BELBUCA. Strategies to reduce the risk include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death.
- While serious, life-threatening or fatal respiratory depression can occur at any time during the use of BELBUCA, the risk is greatest during initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression when initiating therapy with BELBUCA and following dosage increases.
- To reduce the risk of respiratory depression, proper dosing and titration of BELBUCA are essential. Overestimating the dose of BELBUCA when converting patients from another opioid product may result in fatal overdose with the first dose.
- Accidental exposure to BELBUCA, especially in children, can result in respiratory depression and death due to an overdose of buprenorphine. Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.
- Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.
- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with BELBUCA. Also consider prescribing naloxone based on the patient's risk factors for overdose or if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone.

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of BELBUCA during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

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

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of BELBUCA with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. Follow patients closely for signs and symptoms of respiratory depression and sedation.

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

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

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

Adrenal Insufficiency

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

QTc Prolongation

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

Severe Hypotension

- BELBUCA may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of BELBUCA. In patients with circulatory shock, BELBUCA may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of BELBUCA in patients with circulatory shock.

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

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

Hepatotoxicity

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

Risk of Overdose in Patients with Moderate or Severe Hepatic Impairment

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

Anaphylactic/Allergic Reactions

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

Withdrawal

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

Risk of Use in Patients with Gastrointestinal Conditions

- BELBUCA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.
- BELBUCA may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders

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

Risks of Use in Cancer Patients with Oral Mucositis

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

Risks of Driving and Operating Machinery

- BELBUCA may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to side effects of BELBUCA and know how they will react to the medication.

ADVERSE REACTIONS

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

Please see Important Safety Information and full Prescribing Information, including Boxed Warning on Addiction, Abuse, and Misuse, and other serious risks, accompanying this piece or at belbuca.com/PI.

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/safety/medwatch.

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Reframe chronic pain* treatment with BELBUCA®

- BELBUCA contains buprenorphine, a Schedule III opioid[4,9]
- Unlike other opioids, buprenorphine appears to exhibit a dose-ceiling effect[4]
- Buccal film technology enhances buprenorphine bioavailability with 12-hour dosing[14]
- Proven efficacy in patients with chronic pain previously taking Schedule II opioids[4]
- Rates of side effects were comparable to placebo in clinical trials[4]
- 7 film strengths provide dosing flexibility[4]

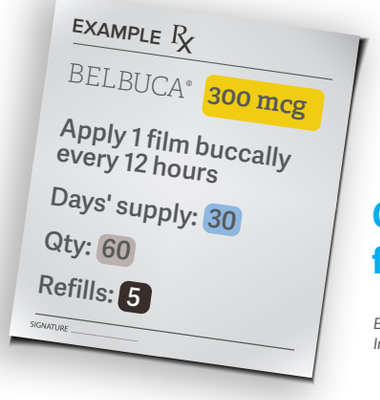
INDICATION

*BELBUCA® (buprenorphine buccal film) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with long-acting opioid formulations, reserve BELBUCA for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- BELBUCA is not indicated as an as-needed (prn) analgesic.

A DEA X-waiver is not required to prescribe BELBUCA[26]



Copay assistance available for eligible patients

Example only. Please refer to page 9 or the full Prescribing Information to determine appropriate dosing.

Please see Important Safety Information and full Prescribing Information, including Boxed Warning on Addiction, Abuse, and Misuse and other serious risks accompanying this piece, or at belbuca.com/PI.

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