Reframe severe and persistent pain* treatment with BELBUCA® (buprenorphine buccal film)

Make BELBUCA your first-choice long-acting opioid*

INDICATION

*BELBUCA (buprenorphine buccal film) is indicated for the management of severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration and because of the greater risks of overdose and death with extended-release/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.

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

IMPORTANT SAFETY INFORMATION ABOUT BELBUCA®

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

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 and reassess all patients regularly for the development of these behaviors and conditions.

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 poses a significant risk of overdose and death.

Accidental Exposure

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

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.

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery.

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.

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.

When do you consider a long-acting treatment option for patients with severe and persistent pain?

Short-acting opioids have potential limitations

- Provide short-term pain relief[1*]
- Multiple daily doses required to achieve around-the-clock relief[1]
- Individual's tolerability issues/side effects[2]
- Nighttime awakenings due to pain[1]

BELBUCA is a long-acting opioid that treats severe and persistent pain when other treatment options, like immediate-release opioids, are inadequate[3†]

- The first and only Schedule III long-acting opioid using buprenorphine buccal film technology[3-5]
- Proven efficacy in opioid-experienced and opioid-naive patients with severe and persistent pain[3]
- 7 dose strengths, allowing for flexible dosing options to reach lowest optimal dose[3]

No associated CDC MME conversion factor with buprenorphine[6‡]

BELBUCA uses BEMA® technology[3,5]

- Allows for 46% to 65% bioavailability of buprenorphine[3]
- Bypasses first-pass metabolism in the gastrointestinal tract[5]
- Releases buprenorphine rapidly into the bloodstream, with peak plasma concentration within 3 hours[3]
- BELBUCA exhibits a mean plasma half-life of 27.6 ±11.2 hours[3]

MucoAdhesive layer contains a dose of buprenorphine and adheres securely within seconds upon contact with the inside of the cheek[3]

Backing layer forms a barrier that helps facilitate one-way flow of medication into buccal mucosa[3,7]

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

*Relief does not imply freedom from pain.

†**There are no head-to-head studies between BELBUCA and short-acting opioids.**

‡CDC MME guidelines are for guidance only and are not a substitute for clinical decision-making. Refer to your state-specific guidelines regarding MME conversions.

BELBUCA exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death.

BEMA=BioErodible MucoAdhesive, CDC=Centers for Disease Control and Prevention, MME=morphine milligram equivalent.

IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

CONTRAINDICATIONS

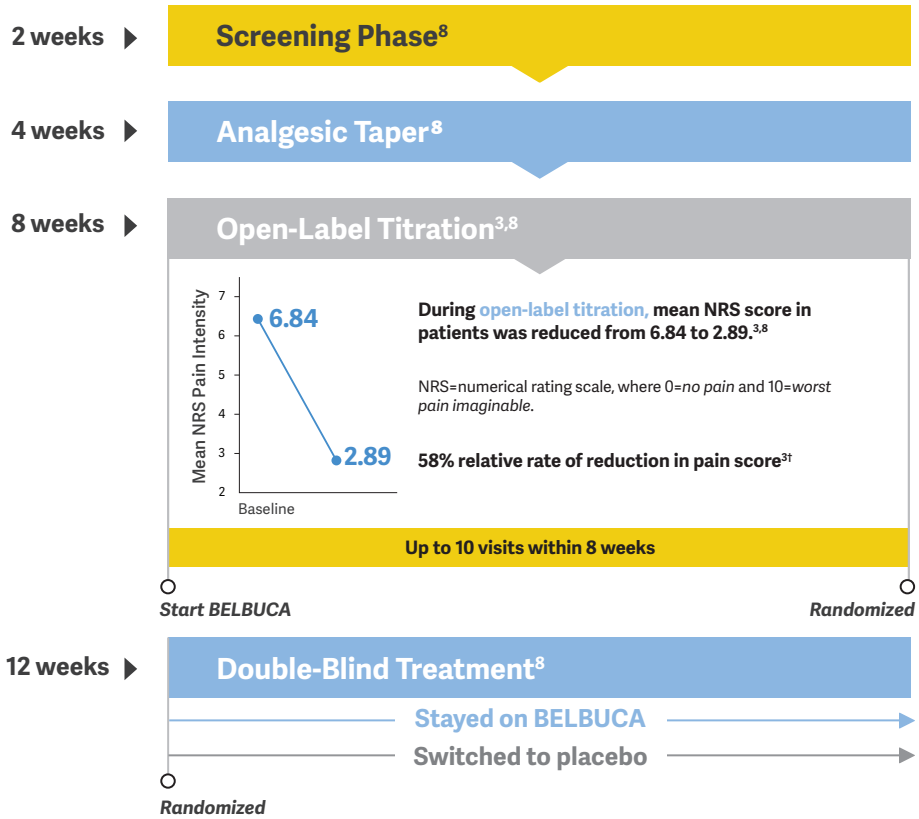
BELBUCA is contraindicated in patients with significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; known or suspected gastrointestinal obstruction, including paralytic ileus; and hypersensitivity (e.g., anaphylaxis)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

In opioid-experienced patients—

The safety and efficacy of BELBUCA were evaluated in a multicenter, double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal study[8]

83% of patients reported poorly controlled pain on their current opioid medications (patients randomized to the double-blind treatment phase)[9,10]

Opioid medications used in ≥5% of patients: hydrocodone (57%), tramadol (34%), oxycodone (19%), and morphine (5%)*



- Inclusion criteria[8]:
  - Opioid-experienced patients (30-160 mg/d MME) with moderate-to-severe chronic low back pain taking around-the-clock opioid analgesics
  - Back pain was non-neuropathic (classes 1 and 2), neuropathic (classes 3-6), or symptomatic for >6 months after low back surgery (class 9) at the time of screening
- Primary efficacy variable was change from baseline to week 12 of double-blind treatment in mean average daily pain intensity scores, using a rating scale of 0 (no pain) to 10 (worst pain imaginable)[3,8]
- Patients were tapered to ≤30-mg daily MME on their current opioid medication within 4 weeks of starting the analgesic taper[3,8]
  - During the analgesic taper phase, patients were permitted HC/APAP 5/325 mg every 6 hours, for a maximum of 4 tablets (20 mg) per day for analgesic rescue medication as needed
- Upon BELBUCA initiation, patients were titrated every 4 to 8 days to optimal dose[8]
  - During the open-label titration phase, patients were permitted to take rescue medication up to 4 doses (1 or 2 tablets) of HC/APAP 5/325 mg per day

***No head-to-head trial vs CII opioids was conducted.**

†Titration of BELBUCA was open-label in nature, and therefore any contribution of a placebo effect to improvement during titration cannot be dissociated.

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. No head-to-head studies vs CII opioids or short-acting opioids were conducted.

HC/APAP=hydrocodone/acetaminophen.

IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

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.

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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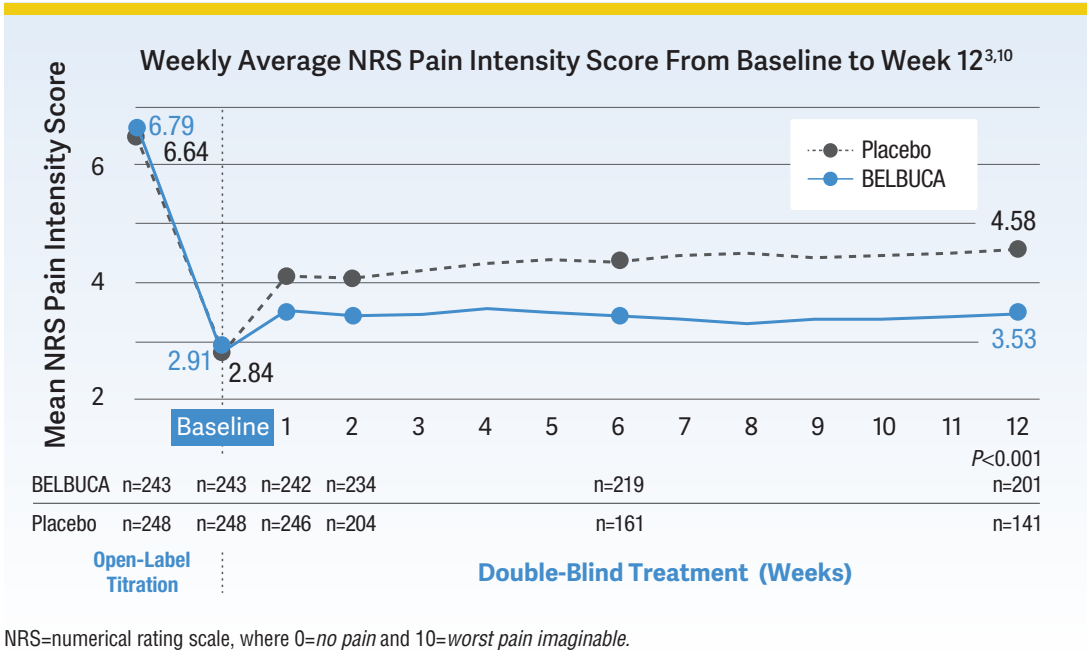
75 • 150 • 300 • 450 • 600 • 750 • 900 mcg

BELBUCA delivered significant and sustained pain relief* to opioid-experienced patients

Statistically significant reductions in numerical rating scale (NRS) pain intensity scores throughout double-blind period and at Week 12[3,8]

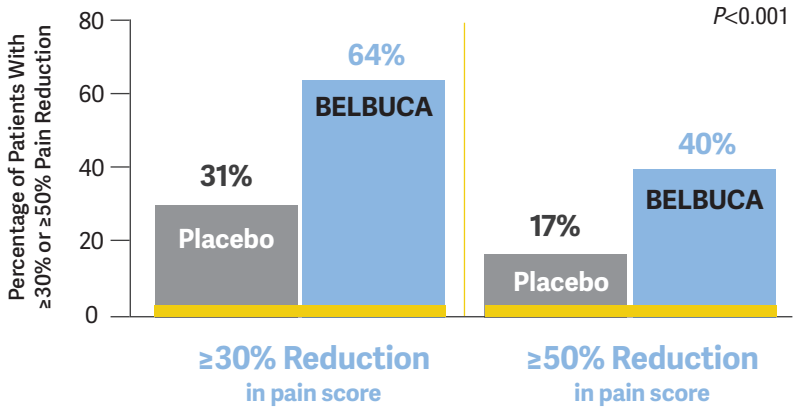


NRS=numerical rating scale, where 0=*no pain* and 10=*worst pain imaginable.*

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.

Significantly more BELBUCA patients achieved both ≥30% and ≥50% reductions in pain scores vs placebo

Pain Score Reductions at Week 12 from prior to open-label titration[3,8]



*Relief is defined as statistically significant reduction in pain, but not necessarily complete freedom from pain.

The efficacy of BELBUCA has been evaluated in three 12-week, double-blind, placebo-controlled clinical trials in opioid-naive and opioid-experienced patients with moderate-to-severe chronic low back pain using pain scores as the primary efficacy variable. Two of these studies 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 with placebo.

IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

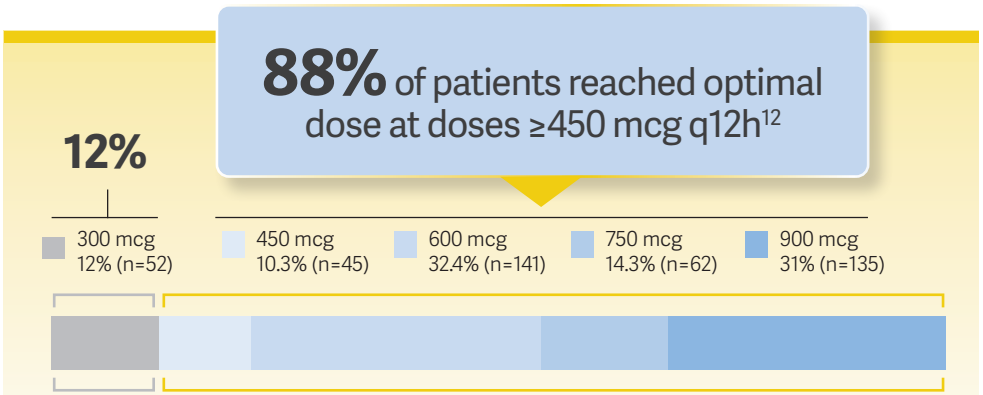
Addiction, Abuse, and Misuse (cont'd)

- 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 prescribing naloxone for the emergency treatment of opioid overdose.

Optimal dose maintained with BELBUCA over 48 weeks[12]

During open-label titration of the long-term safety study, the dose of BELBUCA was titrated until patients reached their optimal dose

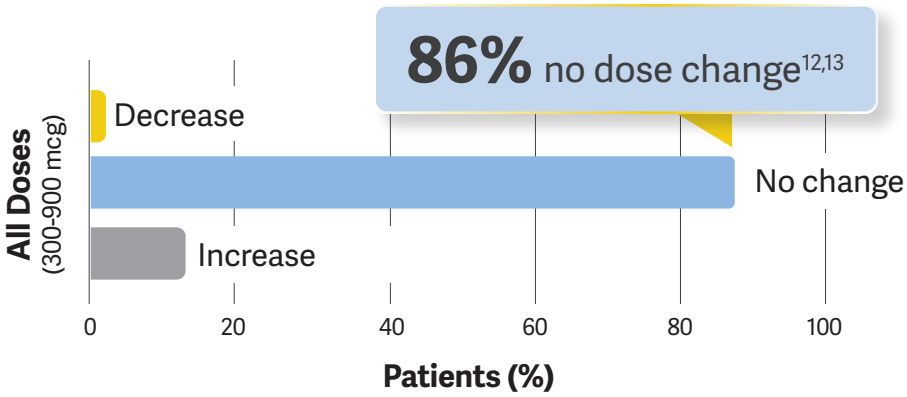
Of the 435 patients who entered the long-term treatment phase—**88% reached their optimal dose of ≥450 mcg**



Need for rescue medication decreased from 3 tablets per day to 1.1 tablets per day on average[12]

- Pain intensity scores remained constant at approximately 3 to 4 during long-term treatment[12]

Once titrated to their optimal dose—**86% of patients maintained analgesic efficacy with no dose change**



Optimal dose was defined as a dose satisfactory for both analgesia and tolerability[12]:

- Without the need for rescue medication, OR
- With no more than 2 tablets of HC/APAP per day

Study Design: The long-term safety, tolerability, and analgesic efficacy of BELBUCA were 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%), loss 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%).

The most commonly reported adverse events (AEs) in the long-term treatment phase included nausea (8.3%), vomiting (5.1%), upper respiratory infections (4.8%), back pain (3.7%), diarrhea (3.4%), nasopharyngitis (3.2%), urinary tract infection (3%), and falls (3%).

There were no reports of respiratory depression in the phase 3, long-term safety study.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of BELBUCA with benzodiazepines or other CNS depressants.

IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

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.

Addiction, Abuse, and Misuse (cont'd)

- Abuse or misuse of BELBUCA by swallowing may cause choking, overdose, and death.
- 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 substance authority for information on how to prevent and detect abuse or diversion of this product.

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BELBUCA tolerability profile

Adverse events (AEs) were compared with placebo in a study of opioid-experienced patients, including patients with severe and persistent pain

AEs Reported in ≥5% of Opioid-Experienced Patients[3]

	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%

Similar AEs were observed in the opioid naive trial. There was a higher incidence of nausea reported in the trial with opioid-naive patients.

- Most common adverse reactions (>5%) include nausea, constipation, headache, vomiting, dizziness, and somnolence[3]
- Discontinuation due to AEs[3,8]:
  - 10.2% (83 of 810 patients) during the open-label titration phase
  - 2% (5 of 254 patients) during the double-blind treatment phase vs 8.2% (21 of 256 patients) in the placebo group
- Discontinuation due to nausea in patients taking BELBUCA was[14]:
  - 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 3 clinical studies of BELBUCA, including the long-term safety study[8,12]**
- **Serious, life-threatening, or fatal respiratory depression may occur with use of BELBUCA, especially during initiation of BELBUCA or following a dose increase[3]**
- **No head-to-head trial vs CII opioids was conducted**

MedDRA=Medical Dictionary for Regulatory Activities, QD=once daily.
For opioid-naive and opioid non-tolerant patients, begin at 75 mcg QD or q12h. Only doses up to 450 mcg q12h were studied in opioid-naive patients.

IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

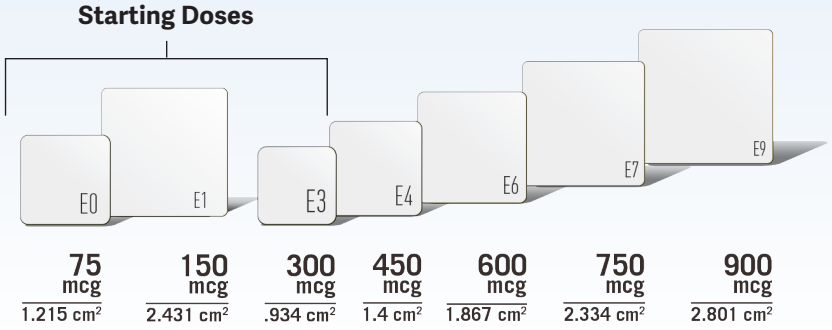
Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. 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.

BELBUCA offers more dosing options and strengths than transdermal buprenorphine

Individualize treatment with 7 dose strengths and q12h dosing[3]

Titrate BELBUCA to a dose that provides adequate analgesia and minimizes adverse reactions[3]



BELBUCA dosing and administration vs transdermal buprenorphine in patients with severe and persistent pain

	BELBUCA[3,15]	Transdermal buprenorphine[15-17]
Total daily dose of prior opioid*	**0–160 MME**	0–80 MME
Titration interval	**4 days**	3 days
Method of application	**Apply to inside of cheek every 12 hours. Typically dissolves in 30 minutes**	Apply to skin at 1 of 8 designated sites every 7 days. Do not apply to same site for 21 days
Bioavailability	**46%–65%**	~15%
Total no. of dose strengths	**7**	5
Maximum dose	**900 mcg**	20 mcg/hr
Dosing interval	**q12h**	q7d
Dose options and strengths	**75 mcg** **150 mcg** **300 mcg** **450 mcg** **600 mcg** **750 mcg** **900 mcg**	5 mcg/hr 7.5 mcg/hr 10 mcg/hr 15 mcg/hr 20 mcg/hr

*Total daily MME of the opioid medications patients took prior to enrolling in clinical trials.
There are no head-to-head studies comparing pharmacokinetics, bioavailability, safety, and efficacy of the 2 products.
Transdermal buprenorphine hourly dosing: 0.005 mg/hr; 0.0075 mg/hr; 0.01 mg/hr; 0.015 mg/hr; 0.02 mg/hr.

Table is based on information included in the full Prescribing Information for each product.

IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

Life-Threatening Respiratory Depression (cont'd)

- 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.

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Starting patients on BELBUCA

A stepwise approach to transition appropriate opioid-experienced patients to BELBUCA[3]

Step 1

- Identify the current daily MME
- Taper opioid-experienced patients

Step 2

Determine the appropriate BELBUCA starting dose based on the patient's total daily opioid dose prior to taper[3]

Step 3

After initiation, proceed with individual titration in increments of 150 mcg[3]

- Titration should occur no more frequently than every 4 days, with doses in q12h intervals
- In patients with severe hepatic impairment or with known or suspected mucositis, reduce starting and titration dose by half that of patients with normal liver function or without mucositis

FIND PREVIOUS DOSE		DETERMINE BELBUCA STARTING DOSE	TITRATE BELBUCA TO OPTIMAL DOSE with appropriate q12h doses†					
			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	Taper opioid-experienced patients' current opioid dose to ≤30-mg MME daily	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 opioid-naive and opioid non-tolerant patients, begin at 75 mcg QD or q12h. Only doses up to 450 mcg q12h were studied in opioid-naive patients.

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. BELBUCA can be prescribed along with short-acting opioids.[3]

Optimal dose was defined as a dose satisfactory for both analgesia and tolerability[12]:

- Without the need for rescue medication, OR
- With no more than 2 tablets of HC/APAP per day

*Maximum dose is 900 mcg every 12 hours. Do not exceed due to the potential for QTc interval prolongation. If pain is not managed at this maximum dose, or for patients previously taking >160 MME, consider an alternate analgesic.

†**Only doses up to 450 mcg q12h were studied in opioid-naive patients. For opioid-naive and opioid non-tolerant patients, begin at 75 mcg QD or q12h for at least 4 days before continuing in increments of 150 mcg q12h.** 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 plasma. **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.**

IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

Life-Threatening Respiratory Depression (cont'd)

- 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.

INDICATION

BELBUCA (buprenorphine buccal film) is indicated for the management of severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.

Limitations of Use

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

IMPORTANT SAFETY INFORMATION ABOUT BELBUCA®

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Accidental Exposure

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

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.

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery.

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.

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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 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 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 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 substance authority for information on how to prevent and detect abuse or diversion of this product.

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. 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. 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.

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IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with BELBUCA. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered.
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone.

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 including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, 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.
- 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 prescribing naloxone for the emergency treatment of opioid overdose.
- 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.

Neonatal Opioid Withdrawal Syndrome (NOWS)

- 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 NOWS and manage accordingly. Advise pregnant women using opioids for an extended period of the risk of NOWS and ensure that appropriate treatment will be available.

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.

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.

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. 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).

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 to younger, healthier patients.
- Regularly evaluate patients, 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 nonspecific 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.

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). 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.

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 periodically reassess during treatment with BELBUCA.

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

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.

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.

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.

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.

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.

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 carefully for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

ADVERSE REACTIONS

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

Please see full Prescribing Information, including Boxed Warning 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.

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

Reframe severe and persistent pain* treatment with BELBUCA

BELBUCA is a long-acting opioid that treats severe and persistent pain when other treatment options, like immediate-release opioids, are inadequate[3†]

- The first and only Schedule III long-acting opioid using buprenorphine buccal film technology[3-5]
- Proven efficacy in opioid-experienced and opioid-naive patients with severe and persistent pain[3]
- 7 dose strengths, allowing for flexible dosing options to reach lowest optimal dose[3]

No associated CDC MME conversion factor with buprenorphine[6‡]

†There are no head-to-head studies between BELBUCA and short-acting opioids.
‡CDC MME guidelines are for guidance only and are not a substitute for clinical decision-making. Refer to your state-specific guidelines regarding MME conversions.

COPAY SAVINGS§ available for eligible commercially insured patients

BELBUCA is preferred by most top Commercial health plans and pharmacy benefit managers, which means the lowest branded copays.[18]

§For commercial patients only. Please see Program Terms, Conditions, and Eligibility Criteria at www.Belbuca.com or scan the QR code. Maximum savings limit applies; patient out-of-pocket expense may vary.

INDICATION

*BELBUCA (buprenorphine buccal film) is indicated for the management of severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration and because of the greater risks of overdose and death with extended-release/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.

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 reassess all patients regularly for the development of these behaviors and conditions.

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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