



When short-acting opioids are inadequate...

**Choose BELBUCA first**  
for proven pain relief\*



## INDICATION

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

### Limitations of Use

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

## IMPORTANT SAFETY INFORMATION ABOUT BELBUCA®

### WARNING: 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)

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

#### 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](https://www.belbuca.com/pi).

# When it's time to consider a long-acting treatment option, what are your goals for patients with severe and persistent pain?



Provide consistent pain relief<sup>1,2</sup>



Reduce the number of short-acting opioids taken daily to adequately control pain



Lower their morphine milligram equivalent (MME) doses<sup>3,4\*</sup>

\*The CDC guideline states that, in most cases, there is no further benefit (in pain relief or function) from escalating opioid therapy to  $\geq 50$  MME/day. Increasing opioids beyond 50 MME/day exposes the patient to a progressively higher risk of misuse/addiction and physical complications of therapy without further clinical benefit. Recommendations are voluntary and are intended to support, not supplant, individualized, person-centered care. Flexibility to meet the care needs and the clinical circumstances of a specific patient is paramount.

## Make BELBUCA your first choice long-acting opioid for the treatment of severe and persistent pain<sup>5</sup>



### BUCCAL DELIVERY

The first and only Schedule III long-acting opioid using BEMA<sup>®</sup> buccal film technology to deliver buprenorphine<sup>5-7</sup>



### PROVEN EFFICACY

Significant and sustained pain relief in opioid-experienced patients and patients who are not opioid tolerant<sup>5</sup>



### FLEXIBLE DOSING

7 dose strengths, allowing for flexible dosing options to start patients at the right dose and titrate to the optimal dose<sup>5</sup>



**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.<sup>5</sup>**

No associated CDC MME conversion factor with buprenorphine<sup>3</sup>

CDC MME guidelines provide direction but should not replace clinical judgment. Refer to your state-specific guidelines regarding MME conversions.

BEMA=BioErodible MucoAdhesive; CDC=Centers for Disease Control and Prevention.

### IMPORTANT SAFETY INFORMATION ABOUT BELBUCA<sup>®</sup>

#### 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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## In opioid-experienced patients

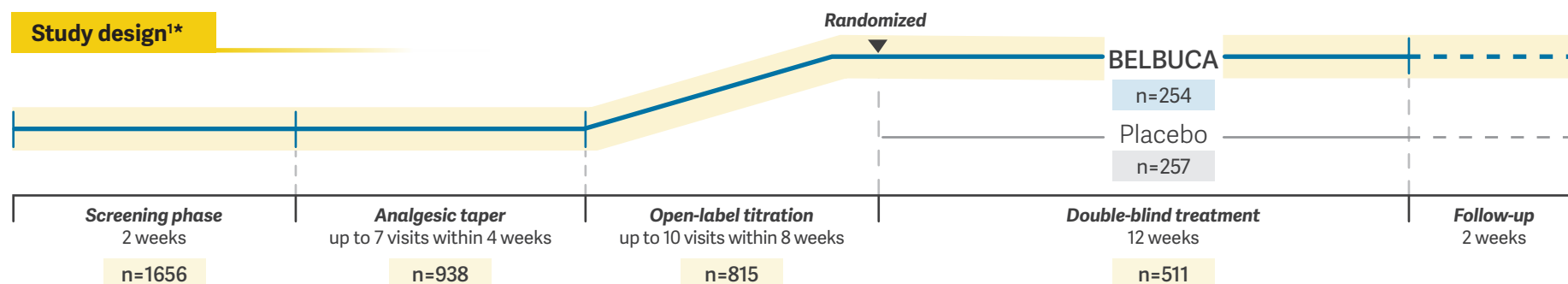
**The efficacy and safety of BELBUCA were evaluated in a 12-week, multicenter, double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal study<sup>1</sup>**

 **83%**

**OF PATIENTS REPORTED POORLY CONTROLLED PAIN ON THEIR CURRENT OPIOID MEDICATIONS AT SCREENING** (of the patients randomized to the double-blind treatment phase)<sup>8,9</sup>

- Opioid medications used in ≥5% of patients: hydrocodone (57%), tramadol (34%), oxycodone (19%), and morphine (5%)
- No head-to-head studies vs CII opioids or short-acting opioids were conducted

### Study design<sup>1\*</sup>



**Analgesic taper:** Patients were tapered to ≤30-mg daily MME on their current opioid medication within 4 weeks of starting the analgesic taper<sup>1,5</sup>

**Open-label titration:** Patients were titrated every 4 to 8 days to optimal dose<sup>1</sup>

**Double-blind treatment:** Patients were randomized to either stay on BELBUCA or be switched to placebo<sup>1</sup>

— 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)<sup>1,5</sup>

**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.**

\*Inclusion criteria included opioid-experienced patients (30-160 mg/day 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.<sup>1</sup>

NRS=numerical rating scale.

## 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. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use.

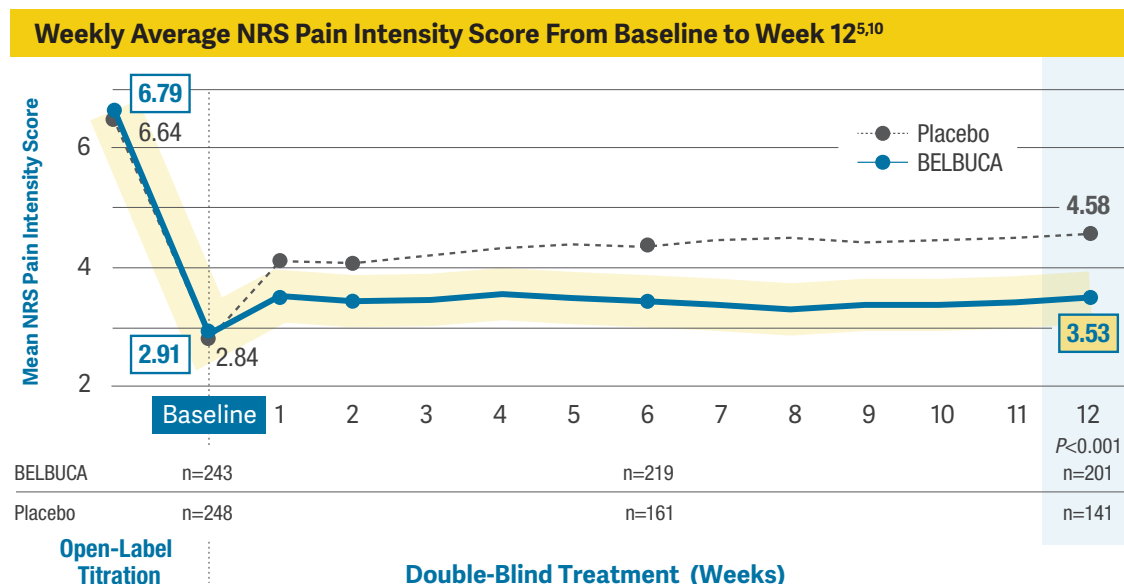
  
**BELBUCA®**  
(buprenorphine buccal film)  
75 • 150 • 300 • 450 • 600 • 750 • 900 mcg

# Significant and sustained pain relief with BELBUCA<sup>5,10\*</sup>

Mean NRS score was reduced from 6.8 to 2.9 during open-label titration

**↓ 58%**

RELATIVE RATE OF REDUCTION IN PAIN SCORE<sup>1,5†</sup>



## Primary Endpoint

**STATISTICALLY SIGNIFICANT REDUCTIONS** in NRS pain intensity scores throughout double-blind period and at Week 12<sup>5,10</sup>

## Secondary Endpoint: Week 12 vs prior to titration

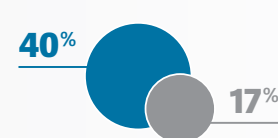
### MORE THAN TWICE AS MANY PATIENTS

ACHIEVED BOTH **≥30% AND ≥50% REDUCTIONS IN PAIN SCORE VS PLACEBO AT WEEK 12 VS PRIOR TO TITRATION<sup>1,5</sup>**

Percentage of patients reaching a **≥30% reduction** in pain score at Week 12 ( $P \leq 0.001$ )



Percentage of patients reaching a **≥50% reduction** in pain score at Week 12 ( $P \leq 0.001$ )



● BELBUCA  
● Placebo

\*Relief is defined as statistically significant reduction in pain (NRS Pain Score), but not necessarily complete freedom from pain.

†Titration of BELBUCA was open-label in nature, and therefore any contribution of a placebo effect to improvement during titration cannot be dissociated. During open-label titration, the dose of BELBUCA was titrated every 4 to 8 days until patients reached their optimal dose, on average, in 24.5 days.<sup>1</sup>

The efficacy of BELBUCA has been evaluated in three 12-week, double-blind, placebo-controlled clinical trials in opioid-naïve (Study 308, Rauck RL, et al. *Postgrad Med.* 2016) 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.<sup>5</sup>

## IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

### WARNINGS AND PRECAUTIONS (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.

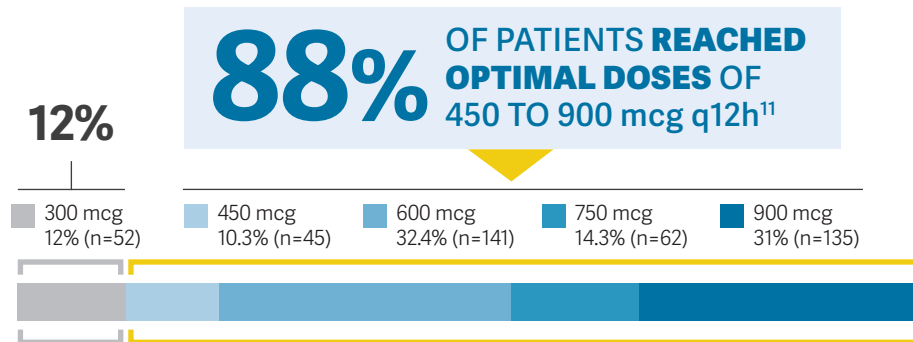
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# Optimal dose of BELBUCA over 48 weeks

During open-label titration of the long-term safety study, the dose of BELBUCA was titrated until patients reached their optimal dose<sup>11</sup>

Of the 435 patients who entered the long-term treatment phase

88% reached an optimal dose of  $\geq 450$  mcg

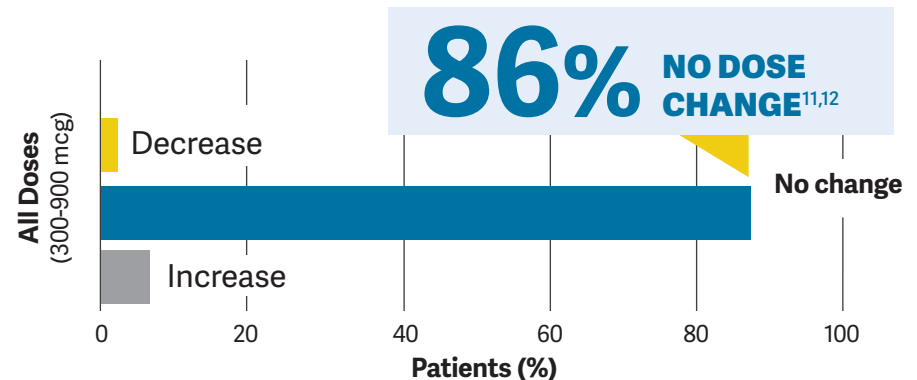


Need for rescue medication decreased from 3 tablets per day during titration to 1.1 tablets per day during the long-term treatment period on average<sup>11</sup>

- Pain intensity scores remained consistent at an NRS score of approximately 3 to 4 during long-term treatment<sup>11</sup>

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<sup>11</sup>:

- Without the need for rescue medication, OR
- No more than 2 tablets (5/325 mg) per day of HC/APAP

The distribution of optimal doses achieved in this study is observational, and not a defined study endpoint.<sup>11</sup>

**Study Design:** The long-term safety, tolerability, and analgesic efficacy of BELBUCA were evaluated in an open-label, single-arm study in opioid-naïve and opioid-experienced patients with moderate to severe chronic pain. The primary objective was to determine the 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%).<sup>11</sup>

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%), headache (4.4%), constipation (3.9%), 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. 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.<sup>11</sup>

HC/APAP=hydrocodone/acetaminophen.

## IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

### WARNINGS AND PRECAUTIONS (cont'd)

#### Addiction, Abuse, and Misuse (cont'd)

- Consider recommending or prescribing an opioid overdose reversal agent.
- Abuse or misuse of BELBUCA by swallowing may cause choking, overdose, and death.

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

# 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 Patients: Opioid-Experienced<sup>5</sup>

|                          | 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%             |

- Most common adverse reactions (>5%) include nausea, constipation, headache, vomiting, dizziness, and somnolence<sup>5</sup>

MedDRA=Medical Dictionary for Regulatory Activities.

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

- There were no reports of respiratory depression in the **pivotal phase 3 clinical studies of BELBUCA, including the long-term safety study**<sup>1,11</sup>
- Serious, life-threatening, or fatal respiratory depression **may occur with use of BELBUCA, especially during initiation of BELBUCA or following a dose increase**<sup>5</sup>
- Discontinuation due to AEs<sup>1,5</sup>:
  - During the open-label titration phase: 10.2% (83 of 810 patients)
  - During the double-blind phase: 2% (5 of 254 patients) in the BELBUCA group and 8.2% (21 of 256 patients) in the placebo group
- Discontinuation due to nausea in patients taking BELBUCA was<sup>13</sup>:
  - 2.6% (21 of 810 patients) during the open-label titration phase
  - 0.4% (1 of 254 patients) during the double-blind treatment phase
- **No head-to-head trial vs CII opioids was conducted**
- Because clinical trials are conducted under widely **varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice**

## IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

### WARNINGS AND PRECAUTIONS (cont'd)

#### Addiction, Abuse, and Misuse (cont'd)

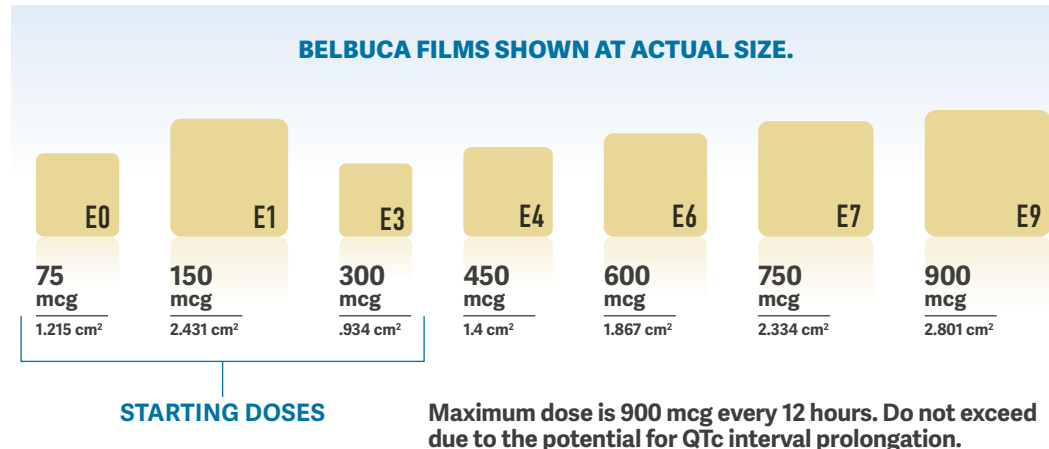
- Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing BELBUCA. Strategies to reduce the risk include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage 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 offers more dosing options and strengths than transdermal buprenorphine

7 dose strengths to identify your patients' optimal dose for treating severe and persistent pain<sup>5</sup>

Titrate BELBUCA to a dose that provides adequate analgesia and minimizes adverse reactions<sup>5</sup>



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.

Appropriate patients inadequately managed on their current therapy up to 160 MME can be transitioned to BELBUCA.<sup>5</sup>



The first and only Schedule III opioid using buprenorphine buccal film technology<sup>5-7</sup>

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

|                                   | BELBUCA <sup>5,14</sup>                                                                                                                                                                | Transdermal buprenorphine <sup>15,16</sup>                                                                                                                                                                                                           |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Total daily dose of prior opioid* | 0-160 MME                                                                                                                                                                              | 0-80 MME                                                                                                                                                                                                                                             |
| Bioavailability                   | 46%-65%                                                                                                                                                                                | ~15%                                                                                                                                                                                                                                                 |
| Half-life                         | 27.6 hours                                                                                                                                                                             | 26 hours <sup>†</sup>                                                                                                                                                                                                                                |
| Total number of dose strengths    | 7                                                                                                                                                                                      | 5                                                                                                                                                                                                                                                    |
| Maximum dose                      | 900 mcg                                                                                                                                                                                | 20 mcg/hr                                                                                                                                                                                                                                            |
| Dosing interval                   | q12h                                                                                                                                                                                   | q7d                                                                                                                                                                                                                                                  |
| Titration interval                | 4 days                                                                                                                                                                                 | 3 days                                                                                                                                                                                                                                               |
| Method of application             | <p>Apply to inside of cheek every 12 hours. Typically dissolves in 30 minutes</p> <p>Avoid eating or drinking until the film is dissolved</p> <p>Wait 1 hour before brushing teeth</p> | <p>Apply to skin at 1 of 8 designated sites every 7 days. Do not apply to same site for 21 days</p> <p>Apply to hairless or nearly hairless skin site</p> <p>Avoid exposure to heat (hot baths, sunbathing, hot tubs, saunas, heating pads, etc)</p> |

Table is based on information included in the full Prescribing Information for each product. **There are no head-to-head studies comparing pharmacokinetics, bioavailability, safety, and efficacy of the 2 products.**

\*Total daily MME of the opioid medications patients took prior to enrolling in clinical trials.

<sup>†</sup>Following patch removal.

## IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

### WARNINGS AND PRECAUTIONS (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 overdose reversal agents, depending on the patient's clinical status. Carbon dioxide (CO<sub>2</sub>) 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®**  
(buprenorphine buccal film)  
75 • 150 • 300 • 450 • 600 • 750 • 900 mcg

# Start at the **right** dose, titrate to the **optimal** dose of BELBUCA<sup>5</sup>

**Step 1:**

**START**

- STARTING DOSE:** Determine the appropriate BELBUCA starting dose based on the **opioid-experienced** patient's total daily opioid dose prior to taper<sup>5</sup>
- TAPER:** Once the current daily MME is identified, taper to ≤30 mg oral MME daily prior to initiating the appropriate BELBUCA starting dose<sup>5</sup>

| PREVIOUS DOSE (oral MME) | STARTING DOSE  |
|--------------------------|----------------|
| 30–89 mg ▶               | 150 mcg q12h ▶ |
| 90–160 mg ▶              | 300 mcg q12h ▶ |

**Step 2:**

**TITRATE**

After initiation, proceed with individual titration in increments of 150 mcg<sup>5</sup>

- 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

| TITRATE BELBUCA TO OPTIMAL DOSE WITH APPROPRIATE Q12H DOSES* |         |         |         |         |
|--------------------------------------------------------------|---------|---------|---------|---------|
| 1                                                            | 2       | 3       | 4       | 5       |
| 300 mcg                                                      | 450 mcg | 600 mcg | 750 mcg | 900 mcg |
| 450 mcg                                                      | 600 mcg | 750 mcg | 900 mcg |         |

**For patients who are not opioid tolerant, initiate treatment at 75 mcg QD or, if tolerated, every 12 hours. If necessary, titrate to 150 mcg and then in increments of 150 mcg. Only doses up to 450 mcg q12h were studied in patients who were not opioid tolerant.<sup>5</sup>**

**Optimal dose was defined as a dose satisfactory for both analgesia and tolerability<sup>11</sup>:**

- Without the need for rescue medication, OR
- With no more than 2 tablets of HC/APAP 5/325 mg per day

No associated CDC MME conversion factor with buprenorphine<sup>3</sup>

+

−

×

=

**DOSING CALCULATOR**  
Scan code to help determine current dose and BELBUCA starting dose.



\*As a partial agonist, buprenorphine is not expected to be associated with overdose in the same dose-dependent manner as full agonist opioids. Maximum dose is 900 mcg every 12 hours. Do not exceed due to the potential for QTc interval prolongation. It is safer to underestimate a patient's dosage and provide rescue medication than to overestimate the 24-hour buprenorphine dosage and manage an adverse reaction due to an overdose. 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.<sup>5</sup>

**Please see Prescribing Information for full dosing and titration information.**

**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.**

QD=once daily.

**IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)**

**WARNINGS AND PRECAUTIONS (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.

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## INDICATION

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### Limitations of Use

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- BELBUCA is not indicated as an as-needed (prn) analgesic.

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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)

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

#### 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.**

## 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

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appropriately prescribed BELBUCA. Addiction can occur at recommended dosages and if the drug is misused or abused. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use.

- Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing BELBUCA and reassess all patients receiving BELBUCA for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as BELBUCA, but use in such patients necessitates intensive counseling about the risks and proper use of BELBUCA, along with frequent reevaluation for signs of addiction, abuse, or misuse.
- Consider recommending or prescribing an opioid overdose reversal agent.
- 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 overdose reversal agents, depending on the patient's clinical status. Carbon dioxide (CO<sub>2</sub>) 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.

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

- Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient.
- Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).

  
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## IMPORTANT SAFETY INFORMATION ABOUT BELBUCA® (cont'd)

### WARNINGS AND PRECAUTIONS (cont'd)

#### Life-Threatening Respiratory Depression (cont'd)

- There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.
- Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered.

#### 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, gabapentinoids [gabapentin or pregabalin], and other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.
- If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the

opioid analgesic, and titrate based on clinical response. Inform patients and caregivers of this potential interaction and educate them on signs and symptoms of respiratory depression (including sedation).

- If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent.
- 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](http://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](http://www.opioidanalgesicrems.com). The FDA Blueprint can be found at [www.fda.gov/OpioidAnalgesicREMSBlueprint](http://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<sub>2</sub> retention (e.g., those with evidence of increased intracranial pressure or brain tumors), BELBUCA may reduce respiratory drive, and the resultant CO<sub>2</sub> 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 Gastrointestinal Complications

- BELBUCA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.
- BELBUCA may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Regularly evaluate patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.
- Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases.
- Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain) and, if necessary, adjust opioid therapy as clinically appropriate.

### 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  $\leq 15$  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 rapidly reduce or abruptly discontinue BELBUCA in a patient physically dependent on opioids. When discontinuing BELBUCA in a physically dependent patient, gradually taper the dosage. Rapid tapering of buprenorphine in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain.
- 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 ( $\geq 5\%$ ) reported by patients treated with BELBUCA in the clinical trials were nausea, constipation, headache, vomiting, fatigue, dizziness, and somnolence.

**See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at [BELBUCA.com/pi](https://www.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](https://www.fda.gov/safety/medwatch).**

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When short-acting opioids are inadequate...

## Choose BELBUCA first for proven pain relief<sup>\*†</sup>

✓ **The first and only Schedule III long-acting opioid** using buprenorphine buccal film technology<sup>5-7</sup>

✓ **Proven efficacy** in opioid-experienced patients and patients who are not opioid tolerant<sup>5</sup>

✓ **7 dose strengths**, allowing for flexible dosing options to reach the optimal dose<sup>5</sup>

No associated CDC MME conversion factor with buprenorphine<sup>3‡</sup>

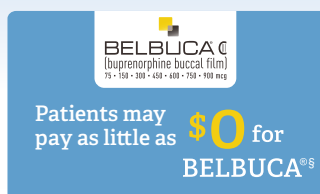
<sup>†</sup>There are no head-to-head studies between BELBUCA and short-acting opioids.

<sup>‡</sup>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. Assess each patient's risk prior to prescribing BELBUCA, and reassess all patients regularly for the development of these behaviors and conditions.

**~9 TIMES OUT OF 10, WHEN  
THE RIGHT FORM IS USED,  
BELBUCA WILL BE APPROVED AND  
PICKED UP BY THE PATIENT<sup>17</sup>**

BELBUCA is preferred by most top commercial health plans and pharmacy benefit managers, which means it has the lowest branded copays.<sup>17</sup>



**COPAY SAVINGS<sup>§</sup>** available for eligible commercially insured patients

<sup>§</sup>For commercial patients only. Please see Program Terms, Conditions, and Eligibility Criteria at [www.belbuca.com](http://www.belbuca.com). Maximum savings limit applies; patient out-of-pocket expense may vary.

**SCAN CODE to  
learn how your  
appropriate patients  
may be able to save  
on BELBUCA.**



### INDICATION

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

### Limitations of Use

- Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy, reserve opioid analgesics, including BELBUCA, for use in patients for whom alternative treatment options 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](http://BELBUCA.com/pi).



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