INDICATION

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

Limitations of Use

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

IMPORTANT SAFETY INFORMATION about BELBUCA®

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

Addiction, Abuse, and Misuse

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

Risk Evaluation and Mitigation Strategy (REMS)

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

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

Life-Threatening Respiratory Depression

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

Accidental Exposure

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

Neonatal Opioid Withdrawal Syndrome

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

Risks from Concomitant Use with Benzodiazepines Or Other CNS Depressants

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

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

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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

Life-Threatening Respiratory Depression

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

Neonatal Opioid Withdrawal Syndrome

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

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

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

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

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

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

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

Adrenal Insufficiency

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

Severe Hypotension

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

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

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

Hepatotoxicity

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

Risk of Overdose in Patients with Moderate or Severe Hepatic Impairment

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

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.

Risk of Use in Patients with Gastrointestinal Conditions

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

Increased Risk of Seizures in Patients with Seizure Disorders

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

Risks of Use in Cancer Patients with Oral Mucositis

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

Risks of Driving and Operating Machinery

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

ADVERSE REACTIONS

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

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To report SUSPECTED ADVERSE REACTIONS, contact Collegium Pharmaceutical, Inc. at 1-855-331-5615 or FDA at 1-800-FDA-1088 or www.fda.gov/safety/medwatch.

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(buprenorphine buccal film)
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Make **BELBUCA** your **1st-choice** LAO*

Administration with BEMA® Buccal Film Technology for Moderate to Severe Chronic Pain*

BEMA=BioErodible MucoAdhesive; LAO=Long-Acting Opioid

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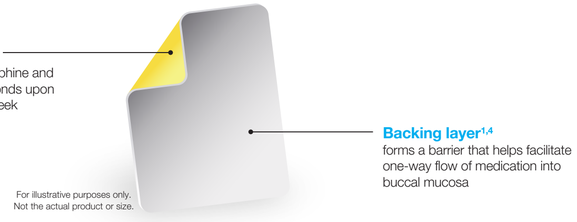
BELBUCA is the first and only long-acting opioid to use buprenorphine buccal film technology[1-3]

BEMA Technology[1,2]

- Allows for 46% to 65% bioavailability of buprenorphine[1]
- Bypasses first-pass metabolism in the gastrointestinal tract[2]
- Releases buprenorphine rapidly into the bloodstream, with peak plasma concentration within 3 hours[1]
- BELBUCA exhibits a mean plasma half-life of 27.6 ±11.2 hours[1]



MucoAdhesive layer[1]
contains a dose of buprenorphine and adheres securely within seconds upon contact with the inside of cheek

Backing layer[1,4]
forms a barrier that helps facilitate one-way flow of medication into buccal mucosa

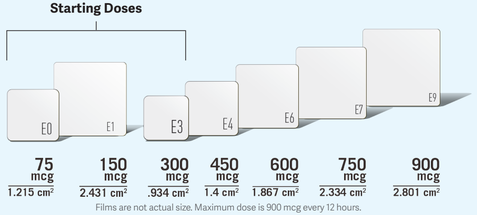
For illustrative purposes only. Not the actual product or size.

belbuca.com

Scan to learn more about applying BELBUCA, and share with appropriate patients.

Individualize treatment with 7 dose strengths[5]

Titrate to the lowest effective dose that generates minimal adverse events (AEs)



Films are not actual size. Maximum dose is 900 mcg every 12 hours.

Continually reevaluate patients receiving BELBUCA to assess the maintenance of pain control and the relative incidence of adverse reactions, and monitor for the development of addiction, abuse, or misuse.

IMPORTANT SAFETY INFORMATION about BELBUCA®

CONTRAINDICATIONS

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

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

Starting your patients on BELBUCA

Use a stepwise approach to transition appropriate opioid-experienced patients to BELBUCA[1]

First, determine:

- Current daily MME, then taper current opioid dose to 30-mg oral MME daily
- Appropriate BELBUCA starting dose based on the patient's total daily opioid dose prior to taper
- For opioid-naive and opioid-intolerant patients, begin at 75 mcg QD or q12h for at least 4 days before continuing in increments of 150 mcg q12h
- Close monitoring is of particular importance when converting from methadone to other opioid agonists, including BELBUCA. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in plasma

After initiation, proceed with individual titration in increments of 150 mcg to lowest effective dose*

- Titration should occur no more frequently than every 4 days, with doses in q12h intervals
- 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
- 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

*Only doses up to 450 mcg q12h were studied in opioid-naive patients.

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

QD=once daily.

†**When transitioning patients to BELBUCA, refer to your state guidelines regarding conversions. Guidelines are for guidance and are not a substitute for clinical decision making.**

‡Optimal dose was defined as a dose satisfactory for both analgesia and tolerability, either without the need for rescue medication or with no more than 2 tablets of HC/APAP per day maintained for at least 7 days.[4]

Serious, life-threatening, or fatal respiratory depression may occur. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and after dose increases with BELBUCA, and adjust the dosing accordingly.

IMPORTANT SAFETY INFORMATION about BELBUCA®

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BELBUCA dosing and administration vs transdermal buprenorphine for patients with moderate to severe chronic pain

There are no head-to-head studies comparing pharmacokinetics, bioavailability, safety, and efficacy of the 2 products.

	BELBUCA[1,5]	Transdermal buprenorphine[5-7]
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 in 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

BELBUCA offers **more dosing options and strengths** than transdermal buprenorphine[1,6]

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

Table is based on information included in the full Prescribing Information for each product.
Transdermal buprenorphine hourly dosing: 0.005 mg/hr; 0.0075 mg/hr; 0.01 mg/hr; 0.015 mg/hr; 0.02 mg/hr.

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References: 1. BELBUCA [Prescribing Information].Stoughton, MA: Collegium Pharmaceutical, Inc.; June 2022. **2.** Data on file, DOF-BL-04. Collegium Pharmaceutical, Inc.; 2015. **3.** Center for Drug Evaluation and Research (U.S.). Orange book: approved drug products with therapeutic equivalence evaluations. US Dept. of Health and Human Services, Food and Drug Administration; 1985. Accessed March 29, 2023. http://purl.access.gpo.gov/GPO/LPS1445 **4.** Hale M, Gimbel J, Rauck R. Buprenorphine buccal film for chronic pain management. *Pain Manag.* 2020;10(4):213-223. **5.** Priestley T, Chappa AK, Mould DR, et al. Converting from transdermal to buccal formulations of buprenorphine: a pharmacokinetic meta-model simulation in healthy volunteers. *Pain Med.* 2018;19(10):1988-1996. **6.** BUTRANS [Prescribing Information]. Stamford, CT: Purdue Pharma L.P. June, 2022. **7.** Wang Y, Cipriano A, Munera C, Harris SC. Dose-dependent flux of buprenorphine following transdermal administration in healthy subjects. *J Clin Pharmacol.* 2016;56(10):1263-1271.

Collegium PHARMACEUTICAL

PP-BEL-US-0066 05/23

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