



## New Data Demonstrate Safety Of Long-Term, Around-The-Clock Treatment With BELBUCA™ (Buprenorphine) Buccal Film For Chronic Pain

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Findings also show sustained pain relief with BELBUCA™ treatment for up to 48 weeks among chronic pain sufferers who require around-the-clock pain relief

DUBLIN, June 3, 2016 /PRNewswire/ -- Endo Pharmaceuticals Inc., a subsidiary of Endo International plc (NASDAQ: ENDP) (TSX: ENL), today announced new data to be presented supporting the safety and tolerability of BELBUCA™ (buprenorphine) buccal film for the long-term management of chronic pain in patients requiring around-the-clock opioids. The findings will be presented during a poster session at the International Conference on Opioids (ICOO 2016) in Boston, which takes place June 5-7.

BELBUCA™ is the first and only buprenorphine formulation developed with a dissolving film that is absorbed through the inner lining of the cheek for chronic pain management. In the Phase 3, open-label study, many patients receiving treatment with BELBUCA™ twice daily reported a low incidence of typical opioid-like side effects such as nausea and vomiting during treatment titration and for up to 48 weeks of daily therapy. The study also found that BELBUCA™ was effective during long-term treatment and provided sustained pain relief throughout the treatment phase (48 weeks) as measured on the numeric rating scale (NRS).

"Many patients living with chronic pain require long-term treatment to control their suffering, so it is important that patients have options to manage their pain," said Martin Hale, M.D., Medical Director, Gold Coast Research, Plantation FL, and one of the study's investigators. "These new findings support the safety and tolerability of treatment with BELBUCA™ across a broad range of dosage strengths. The data may provide healthcare professionals with important information when making treatment decisions for patients living with chronic pain who require daily, around-the-clock opioid treatment and for whom alternative treatment options are inadequate."

The Phase 3, open-label study enrolled 506 patients with moderate to severe chronic pain, requiring continuous around-the-clock opioid treatment who underwent a dose titration period of up to six weeks followed by a long-term treatment phase (48 weeks). Among these patients, 435 patients went on to receive long-term treatment ( $\leq$ 48 weeks) with BELBUCA™ 300  $\mu$ g (n=52), 450  $\mu$ g (n=45), 600  $\mu$ g (n=141), 750  $\mu$ g (n=62) or 900  $\mu$ g (n=135) administered every 12 hours. The primary endpoint was to determine the long-term safety and tolerability of BELBUCA™ (dosed every 12 hours); the secondary endpoint was to determine the long-term efficacy of BELBUCA™ (dosed every 12 hours).

In the safety analysis, adverse events (AEs) ( $>$  3%) occurred in 43.1% and 54.0% of patients during the titration (n=506) and long-term treatment (n=435) phases, respectively. The most common AEs included nausea (10.3%), constipation (5.9%) and headache (3.6%) during the titration phase, and nausea (8.3%), vomiting (5.1%) and upper respiratory tract infection (4.8%) during long-term treatment.

For the efficacy endpoint, the average daily pain intensity score during the treatment phase was between 2.9 and 3.1 on a scale of 0 (no pain) to 10 (worst pain imaginable). In addition, the need for rescue medication to relieve breakthrough pain decreased from an average of 3 tablets in the titration to 1.1 tablets in the long-term treatment phase.

"BELBUCA™ is the first and only buprenorphine buccal film combining the established safety and proven efficacy profile of buprenorphine with a novel buccal film delivery system that adds convenience and flexibility of dosing options and presents a unique approach for chronic pain management," said Susan Hall, Ph.D., Executive Vice President, Chief Scientific Officer and Global Head of Research & Development and Quality at Endo. "With these new study findings, Endo is continuing our focus on addressing an important patient need for safe and effective treatment options for long-term pain relief."

BELBUCA™, distributed and promoted by Endo, was [approved](#) by the U.S. Food and Drug Administration (FDA) in October 2015 for use in patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The FDA approval was based on data from two placebo-controlled, randomized Phase 3 studies showing that BELBUCA™ provided significant improvement in patient-reported pain relief with a low incidence of typical opioid-like side effects.

BELBUCA™ is a mu-opioid receptor partial agonist and a potent analgesic with a long duration of action that utilizes patented BioErodible MucoAdhesive (BEMA®) drug delivery technology from BioDelivery Sciences International, Inc. (NASDAQ: BDSI). Through this unique delivery system, buprenorphine is efficiently and conveniently delivered across the buccal mucosa (inside lining of the cheek). Buprenorphine is a Schedule III controlled substance, meaning that it has been defined as having lower abuse potential than Schedule II drugs, a category that includes most opioid analgesics. Among chronic pain patients taking opioids, the vast majority are on daily doses of 160 mg of oral morphine sulfate equivalent (MSE) or less. BELBUCA™ is available in seven dosage strengths for flexible dosing from 75  $\mu$ g to 900  $\mu$ g every 12 hours, allowing physicians to titrate BELBUCA™ individually for patients to a tolerable dose that provides adequate analgesia with minimal side effects.

For more information, visit [www.Belbuca.com](http://www.Belbuca.com).

**About BELBUCA™**

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 (eg, 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; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; and NEONATAL OPIOID WITHDRAWAL SYNDROME**

#### 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 patients regularly for the development of these behaviors or conditions.

#### 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 pose a significant risk of overdose and death.

#### Accidental Exposure

Accidental exposure to even one dose of BELBUCA™, especially by 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, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

#### **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
- Hypersensitivity (eg, 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.
- 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 or 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 (eg, 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 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.
- Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BELBUCA™ and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.
- Abuse or misuse of BELBUCA™ by swallowing may cause choking, overdose, and death.
- Opioid agonists such as BELBUCA™ are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. 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.
- Contact a local state professional licensing board or state controlled substances 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 buprenorphine, even when used

as recommended. Respiratory depression, from opioid use, 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.

- 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 dose increase. Closely monitor patients for respiratory depression when initiating therapy with BELBUCA™ and following dose 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.

#### **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, somnolence, diarrhea, dry mouth, and upper respiratory tract infection.

[Click here](#) to see additional Important Safety Information.

[Click here](#) to see full Prescribing Information, including boxed Warning.

#### **About Endo International plc**

Endo International plc (NASDAQ: ENDP) (TSX: ENL) is a global specialty pharmaceutical company focused on improving patients' lives while creating shareholder value. Endo develops, manufactures, markets and distributes quality branded and generic pharmaceutical products as well as over-the-counter medications through its operating companies. Endo has global headquarters in Dublin, Ireland, and U.S. headquarters in Malvern, PA. Learn more at [www.endo.com](http://www.endo.com).

#### **About Endo Pharmaceuticals Inc.**

Endo Pharmaceuticals Inc. is focused on developing and delivering high-value branded pharmaceutical products that meet the unmet needs of patients. Endo Pharmaceuticals is an operating company of Endo International plc, a global specialty pharmaceutical company focused on improving patients' lives while creating shareholder value. Learn more at [www.endo.com](http://www.endo.com) or [www.endopharma.com](http://www.endopharma.com).

#### **Cautionary Note Regarding Forward-Looking Statements**

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and Canadian securities legislation, including the statements by Drs. Hale and Hall, and other statements regarding research and development outcomes, efficacy, adverse reactions, market and product potential and availability. Statements including words such as "believes," "expects," "anticipates," "intends," "estimates," "plan," "will," "may," "look forward," "intend," "guidance," "future" or similar expressions are forward-looking statements. Because these statements reflect Endo's current views, expectations and beliefs concerning future events, these forward-looking statements involve risks and uncertainties. Although Endo believes that these forward-looking statements and information are based upon reasonable assumptions and expectations, readers should not place undue reliance on them, or any other forward-looking statements or information in this news release. Investors should note that many factors, as more fully described in the documents filed by Endo with the Securities and Exchange Commission ("SEC") and with securities regulators in Canada on the System for Electronic Document Analysis and Retrieval ("SEDAR), and as otherwise enumerated herein or therein, could affect Endo's future financial results and could cause Endo's actual results to differ materially from those expressed in this press release. The forward-looking statements in this press release are qualified by these risk factors. Endo does not assume any obligation to publicly update any forward-looking statements except as may be required under applicable securities laws.

To view the original version on PR Newswire, visit: <http://www.prnewswire.com/news-releases/new-data-demonstrate-safety-of-long-term-around-the-clock-treatment-with-belbuca-buprenorphine-buccal-film-for-chronic-pain-300279283.html>

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