U.S. FDA Approves BELBUCA™ (buprenorphine) Buccal Film for Chronic Pain Management

October 26, 2015

New treatment option combines proven efficacy and established safety profile of buprenorphine with a novel delivery system that adds convenience and flexibility

DUBLIN and RALEIGH, N.C., Oct. 26, 2015 /PRNewswire/ -- Endo Pharmaceuticals Inc., a subsidiary of Endo International plc (NASDAQ: ENDP) (TSX: ENL), and BioDelivery Sciences International, Inc. (NASDAQ: BDSI), announced today that the U.S. Food and Drug Administration (FDA) has approved BELBUCA™ (buprenorphine) buccal film for use in patients with chronic pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. BELBUCA™, which is the first and only buprenorphine developed with a dissolving film that is absorbed through the inner lining of the cheek for chronic pain management, is expected to be commercially available in the U.S. during the first quarter of 2016 in seven dosage strengths, allowing for flexible dosing ranging from 75 micrograms to 900 micrograms every 12 hours. This enables physicians to individualize titration and treatment based on the optimally effective and tolerable dose for each patient.

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"The availability of new, convenient and flexible treatment options is important for patients whose lives are burdened by chronic pain, a debilitating condition that affects more Americans than diabetes, heart disease and cancer combined," said Richard L. Rauck, M.D., Director of Carolinas Pain Institute, Winston Salem, NC. "BELBUCA™ provides a unique approach for chronic pain management, combining the proven efficacy and established safety of buprenorphine with a novel buccal film delivery system that adds convenience and flexibility. For both opioid-naive and opioid-experienced patients who require around-the-clock treatment and for whom alternative treatment options are inadequate, BELBUCA™ offers appropriate, consistent pain relief and 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 BDSI's patented BioErodible MucoAdhesive (BEMA®) drug delivery technology. 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. With seven dosage strengths up to 160 mg MSE, BELBUCA ™ offers a treatment choice for a wide range of opioid needs in chronic pain sufferers.

"The FDA approval of BELBUCA ™ represents an important and meaningful milestone for Endo Pharmaceuticals, demonstrating our strength in bringing a valuable new therapy from pipeline through approval. Our advancement of BELBUCA ™ also underscores Endo's long-standing heritage of innovation and its commitment to supporting the pain community," said Rajiv De Silva, President and CEO of Endo. "We are proud to add BELBUCA ™ to our diversified portfolio of branded and generic products and we look forward to preparing for the expected U.S. launch of the drug in early 2016."

The FDA approval of BELBUCA™ was based on two double-blind, randomized, placebo-controlled, enriched-enrollment Phase 3 studies in patients with moderate to severe chronic low back pain. In these pivotal trials, a total of 1,559 opioid-experienced (study BUP-307) and opioid-naive (study BUP-308) patients received study drug. The trials included an open-label period in which patients were titrated to a tolerated, effective dose of BELBUCA™ and then randomized to either continue on BELBUCA™ or receive a placebo buccal film.

In both studies, BELBUCA ™ demonstrated a consistent, statistically significant improvement in patient-reported pain relief at every week from baseline to week 12, compared to placebo. The most common adverse reactions (≥5%) reported by patients with BELBUCA ™ in the clinical trials were nausea, constipation, headache, vomiting, fatigue, dizziness, somnolence, diarrhea, dry mouth, and upper respiratory tract infection.

"We are excited about the FDA approval of BELBUCA ™ as we believe it is a testament to the strength of BDSI's partnership with Endo, and our ability to combine our expertise and resources to advance the available options in the treatment of chronic pain," said Dr. Mark A. Sirgo, President and CEO of BDSI. "BELBUCA ™ is uniquely formulated with our BEMA® drug delivery technology that allows for high bioavailability of buprenorphine in the bloodstream, and represents an important new option for patients and healthcare providers."

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.

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 or www.endopharma.com.

About BioDelivery Sciences International
BioDelivery Sciences International, Inc. (NASDAQ: BDSI) is a specialty pharmaceutical company with a focus in the areas of pain management and addiction medicine. BDSI is utilizing its novel and proprietary BioErodible MucoAdhesive (BEMA®) technology and other drug delivery technologies to develop and commercialize, either on its own or in partnership with third parties, new applications of proven therapies aimed at addressing important unmet medical needs.

BDSI's headquarters is located in Raleigh, North Carolina. For more information visit www.bdsi.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 Dr. Rauck, Mr. De Silva and Dr. Sirgo, and other statements regarding research and development outcomes, efficacy, adverse reactions, market and product potential, product approval 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 and BDSI's current views, expectations and beliefs concerning future events, these forward-looking statements involve risks and uncertainties. Although Endo and BDSI believe 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 by BDSI with the SEC, including under the caption "Risk Factors" in Endo's Form 10-K, Form 10-Q and Form 8-K filings, and in BDSI's Form 10-K, Form 10-Q and Form 8-K filings, as applicable, and as otherwise enumerated herein or therein, could affect Endo's and/or BDSI's future financial results and could cause Endo's and/or BDSI's actual results to differ materially from those expressed in this communication. The forward-looking statements in this press release are qualified by these risk factors. Neither Endo nor BDSI assume any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise, except as may be required under applicable securities laws.

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SOURCE Endo Pharmaceuticals Inc.

Endo International plc: Investors/Media: Keri P. Mattox, (484) 216-7912; Media: Heather Zoumas-Lubeski, (484) 216-6829