VIVITROL® and Value of Medication-Assisted Treatment for Opioid Dependence Featured in Study Sponsored by National Institute on Drug Abuse

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DUBLIN--(BUSINESS WIRE)--Nov. 14, 2017-- Results from a National Institute on Drug Abuse (NIDA)-funded study, were published in *The Lancet* today, comparing extended-release naltrexone (VIVITROL®) and buprenorphine-naloxone, two options for opioid dependence. This is the second study published in the past month comparing these two medications and it provides additional evidence supporting the use of VIVITROL as an effective treatment option for patients. Against the backdrop of a national opioid crisis, Medication-Assisted Treatment (MAT) is substantially underutilized. Data from the study reinforce the value of MAT and the distinct differences between two important options for this devastating disease.

VIVITROL represents a different approach to treating opioid dependence. VIVITROL is an injectable, once-monthly, extended-release form of naltrexone, an opioid receptor antagonist. Buprenorphine-naloxone is an opioid partial agonist. In a previously published journal article discussing the NIDA study design, the study investigators observed, “Agonists and antagonists are diametrically opposite in domains ranging from pharmacology to treatment philosophy. Agonists maintain physical tolerance and opioid dependence; antagonists block any opioid effects and are not psychoactive or habit-forming.[1]”

VIVITROL was developed by Alkermes (NASDAQ: ALKS). It was approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol dependence in 2006 and for the prevention of relapse to opioid dependence, following opioid detoxification, in 2010. Since its first approval, more than 350,000 patients have been treated with VIVITROL.

“VIVITROL is an entirely different approach from maintenance therapies. VIVITROL works by blocking opioid receptors in the brain and is the only FDA-approved medication for preventing relapse to opioid dependence, following opioid detoxification,” said Craig Hopkinson, M.D., Chief Medical Officer and Senior Vice President of Clinical Development and Medical Affairs at Alkermes. “This study highlights the importance of detoxification for initiating treatment with VIVITROL. Alkermes is working alongside prominent researchers in the field to determine effective, safe and efficient detoxification strategies for successful induction onto VIVITROL, in order to help healthcare providers manage their patients through this critical transition period.”

“These data confirm and build on the body of evidence supporting the value of Medication-Assisted Treatment, and VIVITROL is an important element of the nation’s response to treating opioid dependence. Addiction is a highly complex disease, and no single treatment option is right for all patients,” said Richard Pops, Chief Executive Officer of Alkermes. “In order to address this epidemic, the treatment system for opioid addiction must evolve to embrace data-driven, patient-centered care customized to the clinical needs of each individual. We remain committed to working alongside healthcare providers, policymakers and public health officials to ensure access to all FDA-approved medications for this underserved population. Patients need greater access to medicines that work.”

We are in the midst of a public health crisis, and only a small percentage of patients suffering from opioid use disorder are getting treatment. Alkermes applauds NIDA’s commitment to advancing research focused on treatment options, as it is effective and significantly underutilized despite the large and growing body of evidence supporting the use of medication to treat the disease.

About Opioid Dependence

A chronic brain disease, opioid dependence is characterized by cognitive, behavioral and physiological symptoms in which an individual continues to use opioids despite significant harm to oneself and others.[2] The use of heroin, an illegal opioid drug, and the non-medical use of FDA-approved opioid analgesics, including prescription pain relievers, represents a growing public health problem in the U.S. According to the 2016 U.S. National Survey on Drug Use and Health, nearly 2 million people aged 18 or older had an opioid use disorder.[3]

About VIVITROL®

VIVITROL (naltrexone for extended-release injectable suspension) is a once-monthly medication for the treatment of alcohol dependence as well as for the prevention of relapse to opioid dependence, following opioid detoxification. VIVITROL is a non-narcotic, non-addictive, once-monthly medication approved for the treatment of opioid dependence. Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support.

IMPORTANT SAFETY INFORMATION

INDICATIONS

VIVITROL® is indicated for:

- Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration.
- Prevention of relapse to opioid dependence, following opioid detoxification.
- VIVITROL should be part of a comprehensive management program that includes psychosocial support.

CONTRAINDICATIONS

VIVITROL is contraindicated in patients:

- Receiving opioid analgesics
- With current physiologic opioid dependence
- In acute opioid withdrawal
- Who have failed the naloxone challenge test or have a positive urine screen for opioids
- Who have exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent

WARNINGS AND PRECAUTIONS

Vulnerability to Opioid Overdose:

- After opioid detoxification, patients are likely to have a reduced tolerance to opioids. VIVITROL blocks the effects of exogenous opioids for approximately 28 days after administration. As the blockade wanes and eventually dissipates completely, use of previously tolerated doses of opioids could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.).
- Cases of opioid overdose with fatal outcomes have been reported in patients who used opioids at the end of a dosing interval, after missing a scheduled dose, or after discontinuing treatment. Patients and caregivers should be told of this increased sensitivity to opioids and the risk of overdose.
- Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. The plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids.
- Any attempt by a patient to overcome the VIVITROL blockade by taking opioids may lead to fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade.

Injection Site Reactions:

- VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe.
- Injection site reactions not improving may require prompt medical attention, including, in some cases, surgical intervention.
- Inadvertent subcutaneous/adipose layer injection of VIVITROL may increase the likelihood of severe injection site reactions.
- Select proper needle size for patient body habitus, and use only the needles provided in the carton.
- Patients should be informed that any concerning injection site reactions should be brought to the attention of their healthcare provider.

Precipitation of Opioid Withdrawal:

- When withdrawal is precipitated abruptly by administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe. Some cases of withdrawal symptoms have been severe enough to require hospitalization, and in some cases, management in the ICU.
- To prevent occurrence of precipitated withdrawal, opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) before starting VIVITROL treatment:

  - An opioid-free interval of a minimum of 7–10 days is recommended for patients previously dependent on short-acting opioids.

  - Patients transitioning from buprenorphine or methadone may be vulnerable to precipitated withdrawal for as long as two weeks.
- If a more rapid transition from agonist to antagonist therapy is deemed necessary and appropriate by the healthcare provider, monitor the patient closely in an appropriate medical setting where precipitated withdrawal can be managed.
- Patients should be made aware of the risk associated with precipitated withdrawal and be encouraged to give an accurate account of last opioid use.

Hepatotoxicity:

- Cases of hepatitis and clinically significant liver dysfunction have been observed in association with VIVITROL. Warn patients of the risk of hepatic injury; advise them to seek help if experiencing symptoms of acute hepatitis. Discontinue use of VIVITROL in patients who exhibit acute hepatitis symptoms.

Depression and Suicidality:

- Alcohol- and opioid-dependent patients taking VIVITROL should be monitored for depression or suicidal thoughts. Alert families and caregivers to monitor and report the emergence of symptoms of depression or suicidality.

When Reversal of VIVITROL Blockade Is Required for Pain Management:

- For VIVITROL patients in emergency situations, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required to reverse the VIVITROL blockade, patients should be closely monitored by trained personnel in a setting staffed and equipped for CPR.

Eosinophilic Pneumonia:

- Cases of eosinophilic pneumonia requiring hospitalization have been reported. Warn patients of the risk of eosinophilic pneumonia and to seek medical attention if they develop symptoms of pneumonia.

Hypersensitivity Reactions:

- Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis.

Intramuscular Injections:

- As with any IM injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder.

Alcohol Withdrawal:

- Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

ADVERSE REACTIONS

- Serious adverse reactions that may be associated with VIVITROL therapy in clinical use include severe injection site reactions, eosinophilic pneumonia, serious allergic reactions, unintended precipitation of opioid withdrawal, accidental opioid overdose, and depression and suicidality.
- The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (ie, those occurring in ≥5% and at least twice as frequently with VIVITROL than placebo) include nausea, vomiting, injection site reactions (including induration, pruritus, nodules, and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.
- The adverse events seen most frequently in association with VIVITROL in opioid-dependent patients (ie, those occurring in ≥2% and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

You are encouraged to report side effects to the FDA.

Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see Full Prescribing Information for VIVITROL.

About Alkermes

Alkermes plc is a fully integrated, global biopharmaceutical company developing innovative medicines for the treatment of central nervous system (CNS) diseases. The company has a diversified commercial product portfolio and a substantial clinical pipeline of product candidates for chronic diseases that include schizophrenia, depression, addiction and multiple sclerosis. Headquartered in Dublin, Ireland, Alkermes plc has an R&D center in Waltham, Massachusetts; a research and manufacturing facility in Athlone, Ireland; and a manufacturing facility in Wilmington, Ohio. For more information, please visit Alkermes' website at www.alkermes.com.

Note Regarding Forward-Looking Statements

Certain statements set forth in this press release constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning the potential therapeutic and commercial value of VIVITROL and improvements to the treatment system for opioid dependence. The company cautions that forward-looking statements are inherently uncertain. Although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: whether clinical results for VIVITROL will be predictive of commercial results and success; and those risks and uncertainties described under the heading "Risk Factors" in the company's Annual Report on Form 10-K for the year

ended Dec. 31, 2016 and Quarterly Reports on Form 10-Q for the quarters ended March 31, 2017 and Sept. 30, 2017 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release.

VIVITROL® is a registered trademark of Alkermes, Inc.

[1] Lee, J.D., et al. (2016). "NIDA Clinical Trials Network CTN-0051, Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT): Study design and rationale." *Contemporary Clinical Trials* 50, 253-264.

[2] DSM-IV-TR, American Psychiatric Association.

[3] SAMHSA. *Behavioral Health Trends in the United States: Results from the 2016 National Survey on Drug Use and Health*.

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