NIDA-Funded Study Evaluating Extended-Release Injectable Naltrexone Plus Bupropion for the Treatment of Methamphetamine Use Disorder Published in New England Journal of Medicine

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DUBLIN, Jan. 14, 2021 /PRNewswire/ -- Results from a National Institute on Drug Abuse (NIDA)-funded study evaluating the efficacy and safety of naltrexone for extended-release injectable suspension (XR-NTX) administered once every three weeks plus oral extended-release bupropion administered daily as a combination treatment for adults with moderate or severe methamphetamine use disorder (MUD) were published today by Dr. Madhukar H. Trivedi et al. in the *New England Journal of Medicine (NEJM)*.[1] This is the second published study evaluating this combination regimen for the treatment of MUD.[2]

The number of adults living with MUD has risen in recent years. In 2019, approximately 1 million adults in the U.S. reported having a methamphetamine use disorder—an increase of more than 50 percent since 2016.[3] Currently, there are no FDA-approved medicines for the treatment of MUD.

"Given the scale and severity of the methamphetamine epidemic in the U.S., we applaud the clinical community's efforts and commitment to advancing research focused on treatment options for this critically underserved patient population," said Craig Hopkinson, M.D., Chief Medical Officer and Executive Vice President of Research & Development at Alkermes. "We're encouraged by the publication of this NIDA-funded study in the *New England Journal of Medicine*, and plan to engage with the FDA to better understand what options may exist for VIVITROL with regards to these data."

VIVITROL® (naltrexone for extended-release injectable suspension) is not approved for the treatment of MUD. VIVITROL, developed by Alkermes (Nasdaq: ALKS), 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. VIVITROL is to be administered once every four weeks as part of a comprehensive management program that includes psychosocial support.

About the ADAPT-2 Study

The "Accelerated Development of Additive Pharmacotherapy Treatment (ADAPT-2) for Methamphetamine Use Disorder" study was a multi-site, double-blind, 12-week trial to evaluate the efficacy and safety of XR-NTX (380 mg every three weeks) plus oral extended-release bupropion (450 mg/day) in adults with moderate or severe MUD. Participants (N=403) with moderate or severe MUD (defined as reported use on at least 18 of the 30 days prior to randomization) were randomized to combination therapy (XR-NTX, 380 mg IM every three weeks, plus bupropion XL, up to 450 mg/d) versus placebo in a two-stage study. Placebo non-responders from stage 1 (6 weeks) were re-randomized in stage 2 for another 6 weeks. The primary outcome was the proportion of "responders," defined as having at least three methamphetamine-negative urine samples out of four samples obtained during weeks 5-6 (for stage 1) or weeks 11-12 (for stage 2). Response rates were higher with XR-NTX plus bupropion than with placebo across both stages (overall weighted treatment effect of 11.1 percentage points; Wald z-test statistic = 4.53; $p < 0.001$; NNT =9), as well as in each stage [stage 1: (16.5% COMB vs. 3.4% PBO); stage 2: (11.4% COMB vs. 1.8% PBO)]. Secondary outcomes also favored treatment with XR-NTX plus bupropion XL as compared to placebo. Adverse events in the combination treatment group included gastrointestinal disorders, tremor, malaise, hyperhidrosis, and anorexia. Serious adverse events occurred in 8 of 223 participants (3.6%) who received XR-NTX plus bupropion in the study. Alkermes provided XR-NTX and matched placebo free of charge for use in this trial under a written agreement with NIDA.

About VIVITROL

VIVITROL® (naltrexone for extended-release injectable suspension) is a once-monthly medication for the treatment of alcohol dependence and for the prevention of relapse to opioid dependence, following opioid detoxification. Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support. For more information, visit www.vivitrol.com.

About Alkermes

Alkermes plc is a fully integrated, global biopharmaceutical company developing innovative medicines in the fields of neuroscience and oncology. The company has a portfolio of proprietary commercial products focused on addiction and schizophrenia, and a pipeline of product candidates in development for schizophrenia, bipolar I disorder, neurodegenerative disorders, and cancer. 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.

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

IMPORTANT SAFETY INFORMATION
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 must be prepared and administered by a healthcare provider.
- 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.
- In the clinical trials, one patient developed an area of induration that continued to enlarge after 4 weeks, with subsequent development of necrotic tissue that required surgical excision.
- 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.
- Precipitated opioid withdrawal has been observed in alcohol-dependent patients in circumstances where the prescriber had been unaware of the additional use of opioids or co-dependence on opioids.

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 including Anaphylaxis:

- Cases of urticaria, angioedema, and anaphylaxis have been observed with use of VIVITROL in the clinical trial setting and in postmarketing use.
- Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis.
- In the event of a hypersensitivity reaction, patients should be advised to seek immediate medical attention in a healthcare setting prepared to treat anaphylaxis. The patient should not receive any further treatment with VIVITROL.

Intramuscular Injections:

- As with any intramuscular 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.

Interference with Laboratory Tests

- VIVITROL may be cross-reactive with certain immunoassay methods for the detection of drugs of abuse (specifically opioids) in urine.
- For further information, reference to the specific immunoassay instructions is recommended.

ADVERSE REACTIONS

- 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), arthralgia, arthritis, or joint stiffness, 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.

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 XR-NTX plus bupropion as a combination treatment for MUD; and the company's plans to engage with the FDA regarding potential options for VIVITROL relating to the ADAPT-2 data. You are cautioned 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 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 the combination treatment of XR-NTX plus bupropion could be shown to be unsafe or ineffective; whether clinical results for this combination treatment will be predictive of results of future clinical studies or real-world results; the outcome of interactions with the FDA related to VIVITROL and the ADAPT-2 data; 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, 2019, the company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 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.

[1] Trivedi MH, Walker R, Ling, W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. *New England Journal of Medicine*, 2021;384:140-53. DOI: 10.1056/NEJMoa2020214

[2] Mooney LJ, Hillhouse MP, Thomas C, et al. Utilizing a Two-stage Design to Investigate the Safety and Potential Efficacy of Monthly Naltrexone Plus Once-daily Bupropion as a Treatment for Methamphetamine Use Disorder. *Journal of Addiction Medicine*, 2016;*10*(4), 236–243. https://doi.org /10.1097/ADM.0000000000000218

[3] SAMHSA. *Behavioral Health Trends in the United States: Results from the 2016 and 2019 National Surveys on Drug Use and Health*. Accessed on Jan. 12, 2021 from: https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health.

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View original content to download multimedia:http://www.prnewswire.com/news-releases/nida-funded-study-evaluating-extended-release-injectable-naltrexone-plus-bupropion-for-the-treatment-of-methamphetamine-use-disorder-published-in-new-england-journal-of-medicine-301208061.html

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