



Alkermes Response to Media Coverage of the Company and VIVITROL

February 25, 2020

At Alkermes, we are committed to patient safety and the appropriate use of our medicines. VIVITROL® (naltrexone for extended-release injectable suspension) is indicated for the prevention of relapse to opioid dependence, after opioid detoxification, when used with psychosocial support such as counseling.¹ It is one of three types of medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of opioid dependence.

We are in the midst of an opioid epidemic. Alkermes believes that all FDA-approved medications for opioid dependence (buprenorphine, methadone and VIVITROL) have a role to play in the treatment paradigm. As each of these medications works differently in the body, they are not interchangeable, and no one medication is right for everyone. Each treatment option plays a fundamentally different role in the treatment of opioid dependence and addresses very different clinical needs, lifestyles and moments in the journey of recovery. For these reasons, Alkermes supports access to all FDA-approved medications for opioid dependence and the importance of patient-centered care (i.e., licensed healthcare professionals applying their independent clinical judgment, working in partnership with their patients, to determine the appropriate treatment plan for each patient).

With this goal in mind, we feel compelled to respond to certain statements in the Boston Globe article appearing on February 24, 2020.

Relapse to opioid dependence can be a complicated treatment issue for people struggling with the disease. The VIVITROL [Prescribing Information](#) and [Medication Guide](#), which accompany the product and which are available on the VIVITROL [website](#), clearly state the product efficacy and safety risks, which includes the increased vulnerability of patients to potentially fatal overdose at the end of a dosing interval, after missing a dose, or after discontinuing VIVITROL due to the reduction of their pre-treatment baseline opioid tolerance.

All three FDA-approved medications for the treatment of opioid dependence, including VIVITROL, are considered first-line treatment options. The FDA, in approving VIVITROL, did not indicate that it only be used as a second-line treatment. The American Society of Addiction Medicine National Practice Guidelines² state, “The choice among available treatment options should be a shared decision between the clinician and the patient.” Additionally, the Treatment Improvement Protocol (TIP) 63,³ *Medications for Opioid Use Disorder* state, “There is no “one size fits all” approach to OUD treatment.” VIVITROL is considered a first-line therapy option for appropriate patients seeking a non-agonist pharmacotherapy. Several studies also support that patients—when adequately informed about all treatment options—indicate an interest in or preference for VIVITROL.^{4,5}

We stand by the efficacy and safety of VIVITROL and the ethical, compliant nature of our marketing practices and interactions with stakeholders across the treatment landscape. We will continue to educate licensed healthcare providers, and the extended treatment teams who support the patient, about VIVITROL. And we will continue to support access to all FDA-approved medications for the treatment of opioid dependence and to advocate for patient-centered care.

References:

¹ Alkermes Inc. VIVITROL® Prescribing Information. Waltham, MA:2019.
<https://www.vivitrol.com/content/pdfs/prescribing-information.pdf>

² Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. *J. Addict. Med.* 2015;9(5):358-367.

³ Substance Abuse and Mental Health Services Administration (SAMHSA). Medications To Treat Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63, Full Document. HHS Publication No. (SMA) 18-5063FULLDOC ed. Rockville, MD 2018.

⁴ Uebelacker LA, Bailey G, Herman D, et al. Patients' Beliefs About Medications are Associated with Stated Preference for Methadone, Buprenorphine, Naltrexone, or no Medication-Assisted Therapy Following Inpatient Opioid Detoxification. *J. Subst. Abuse Treat.* 2016;66:48-53.

⁵ Douaihy A, Akerman SA, Legedza A, et al. Characteristics of Individuals Seeking to Transition From BUP to XR-NTX in a Randomized, Placebo-Controlled Trial. Poster Presented at: American Academy of Addiction Psychiatry (AAAP); 2019; San Diego, CA, USA

About VIVITROL®

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 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.
- 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
 - 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 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.

ADVERSE REACTIONS

- The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (ie, those occurring in $\geq 5\%$ 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 $\geq 2\%$ 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 VIVITROL full [Prescribing Information](#)

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