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November 8, 2017

Dear Senator Harris,

We are in receipt of your letter dated November 6, 2017 requesting information on VIVITROL[®] (naltrexone for extended-release injectable suspension). We intend to cooperate with your request and look forward to providing you and your staff with information about VIVITROL. Your recent letter to Alkermes and quotes that you provided to various news outlets in connection with its release reflect a misperception of VIVITROL and Alkermes that we wish to address.

First, we would like to address the evidence base in support of VIVITROL. VIVITROL was developed in response to a call for long-acting antagonists issued by the National Institute on Drug Abuse in 1976. The FDA approved VIVITROL in 2006 for the treatment of alcohol dependence and in 2010 for the prevention of relapse to opioid dependence following opioid detoxification. VIVITROL underwent a rigorous process to earn FDA approval and has been studied extensively. It has been used by hundreds of thousands of patients, and its safety and effectiveness are a matter of record.

This evidence base has recently expanded with the publication in last month's *Journal of the American Medical Association (JAMA) Psychiatry* of the results of a head-to-head comparison of VIVITROL and buprenorphine, another medication approved for the treatment of opioid dependence. The study found that VIVITROL was as effective as buprenorphine-naloxone when it came to reducing the use of heroin and other illicit opioids. According to the study's author, Lars Tanum, M.D., Ph.D., Associate Professor, Norwegian Centre for Addiction Research at the University of Oslo, Norway, and Head of Research Unit, Department of R&D in Mental Health Services, Akershus University Hospital, Norway:

“To our knowledge, this is the first study comparing the effectiveness of extended-release naltrexone injections with that of daily oral buprenorphine-naloxone, the standard [opioid medication treatment]... Treatment with extended-release naltrexone was as effective as buprenorphine-naloxone in maintaining retention in treatment and reducing the use of heroin [and] other illicit opioids...Extended-release naltrexone should be an available treatment option for opioid dependent individuals.”

Second, we want to address our interactions with law enforcement personnel. The Department of Health and Human Services has issued numerous publications recognizing the important role of the correctional treatment team (including judges, coordinators, attorneys) and encouraging the use of medication-assisted treatment in criminal justice settings, noting that “medications can be an important component of effective drug abuse treatment for offenders” and that “addiction medications are underused in the treatment of drug abusers within the criminal justice system, despite evidence of their effectiveness.” *National Institute on Drug Abuse, Principles of Drug Abuse Treatment for Criminal Justice Populations, A Research-Based Guide (page 23); SAMHSA In Brief, Summer 2014 Volume 8, Issue 1 (page 1).*

As one of only three types of FDA-approved treatments for opioid dependence and as the only treatment indicated for the prevention of relapse to opioid dependence after detoxification, VIVITROL has an important role to play in the treatment of opioid dependence. While Alkermes representatives call primarily on physicians and healthcare personnel, we also educate other stakeholders involved in the treatment of opioid dependence about VIVITROL, including drug courts, criminal justice professionals and the healthcare professionals that are part of the criminal justice treatment team. We interact with



these stakeholders because they are critical members of the treatment ecosystem, many of whom are seeking information on VIVITROL and evolving practices in the treatment of opioid dependence. VIVITROL appeals to the criminal justice setting because it's the only medication approved by the FDA to prevent relapse to opioid dependence following detoxification from opioids. Moreover, it has no risk of abuse and is not associated with diversion, traded or sold illicitly, within or outside of the correctional setting.

In this context, we provide samples of VIVITROL free of charge, upon the written request of the correctional institution and the licensed healthcare provider, for use in those comprehensive criminal justice re-entry programs that include a range of services in addition to the prescribing of VIVITROL for appropriate patients, including ongoing patient support services, and where VIVITROL is provided as a voluntary component of the re-entry program.

To be clear, while VIVITROL occupies its place in the criminal justice system because of its attributes, its use goes beyond this specific population of patients. Every patient deserves access to all medications to treat opioid dependence, and we work with government agencies and elected officials to provide information in support of such access. We know firsthand the stories of patients whose lives have been saved by methadone, buprenorphine and VIVITROL. The question cannot and should not be which one is better. The question is: which treatment for opioid addiction is right for me or my loved one at this moment in time in the course of a vicious, deadly disease, and can I get timely access to treatment?

Unfortunately, unlike in other areas of medicine, without advocacy efforts, access to medicines and treatment can be challenging for patients. As an example, we fully supported the Comprehensive Addiction and Recovery Act – or CARA (which I believe, as Attorney General of California, you endorsed), an important piece of legislation that overwhelmingly passed the House and Senate in a bipartisan manner and was enacted into law in 2016. CARA requires that all office-based opioid addiction providers must have the capacity to offer *all* FDA-approved medications, either directly or by referral. Furthermore, these same providers also need to complete training on all approved options, detoxification, relapse prevention and overdose reversal.

This law seeks to eliminate the deep systemic bias toward opioid replacement therapy in addiction treatment settings without consideration of other treatment options. In examining the current, inadequate treatment system, it is important to note how many treatment centers and practitioners utilize only one form of treatment, and do not provide their patients with alternatives. Why is this the case? This is in stark contrast to other areas of medicine.

The opioid addiction treatment system must change if we are to realize the promise of patient-centered care—care customized to the clinical needs of the patient, regardless of the treatment setting in which the patient is seen. We believe that a comprehensive, patient-centered approach is critical. Our goal is to be part of the national solution in addressing a crisis that is consuming families and entire communities.

We encourage you to truly look into the treatment framework in this country. You will find that it is broken and that we can help. We look forward to working with you to address this epidemic.

Sincerely,

A handwritten signature in black ink, appearing to read "Richard Pops".

Richard Pops



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 $\geq 5\%$ 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 $\geq 2\%$ 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 [Full Prescribing Information](#) for VIVITROL.