VIVITROL® (naltrexone for extended-release injectable suspension)
(See full Prescribing Information at www.VIVITROL.com)

Good Morning, my name is Dr. Paul Thompson, Senior Medical Science Liaison @ Alkermes. Thank you for the opportunity to provide information regarding Vivitrol (naltrexone for extended-release injectable suspension). I will highlight a few clinical and economic points today.

INDICATIONS:1
- **Alcohol Dependence.** VIVITROL is indicated for treatment of alcohol dependence in patients able to abstain from alcohol in an outpatient setting. (06/2006)
- **Opioid Dependence.** VIVITROL is indicated for prevention of relapse to opioid dependence, following opioid detoxification. (10/2010)
- Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support.
- Opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free for 7-10 days prior to VIVITROL administration.

Treatment Guidelines:
- **ASAM – The National Practice Guideline:** For the Use of Medications in the Treatment of Addiction Involving Opioid Use indicates that naltrexone (both oral and extended-release) is recommended for pharmacologic treatment of opioid use disorder. Additionally, clinicians should consider the patient’s preferences, past treatment history, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone in the treatment of addiction involving opioid use disorder.2 Note that the ASAM guidelines utilize the DSM-5 term “opioid use disorder” whereas VIVITROL is indicated for the DMS-4 term “opioid dependence”.
- Although methadone, buprenorphine, and naltrexone are all superior to no treatment in opioid use disorder, less is known about their relative advantages to one another.2

**Place in Therapy:** In medication-assisted treatment for alcohol and opioid dependence, there are several distinct pharmacologic classes available for use.
- VIVITROL is a once-monthly extended release formulation of naltrexone administered by intramuscular injection by a healthcare professional. Naltrexone, an opioid antagonist (blocker), is the active ingredient in VIVITROL.
- VIVITROL is not an opioid replacement therapy and does not maintain physiological opioid dependence. VIVITROL does require opioid detoxification prior to use. In patients physically dependent on opioids, VIVITROL will precipitate acute withdrawal when administered.
- VIVITROL is not a controlled substance. VIVITROL is not associated with development of tolerance or dependence. There is no potential for abuse, and there are no diversion issues.
- VIVITROL is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or alcohol ingestion.
- There is no withdrawal syndrome associated with discontinuation of VIVITROL.

Dosing:
- VIVITROL 380mg I.M. (gluteral) is administered every 4 weeks by a healthcare professional using the provided carton components. VIVITROL must not be administered intravenously or subcutaneously.

Efficacy-Clinical Studies: For further details please refer to full Prescribing Information.

- **Alcohol Dependence.** VIVITROL was evaluated in a 24 week, placebo-controlled, multi-center, double-blind, randomized trial of 624 alcohol-dependent (DSM-IV criteria) outpatients receiving psychosocial support. Subjects treated with VIVITROL 380mg demonstrated a greater reduction in days of heavy drinking than those treated with placebo. Efficacy of VIVITROL 380mg was evident in the first month and maintained over the entire treatment period.
- **Opioid Dependence.** VIVITROL was evaluated in a 24 week, placebo-controlled, multi-center, double-blind, randomized trial of 250 detoxified opioid-dependent (DSM-IV) outpatients receiving psychosocial support. The percentage of subjects achieving opioid-free weeks was significantly greater in the VIVITROL group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the VIVITROL group from Week 5 to Week 24.

The Effectiveness of Injectable Extended-Release Naltrexone (XR-NTX) vs. Daily Buprenorphine-Naloxone (BUP-NX) for Opioid Dependence: A Randomized Non-Inferiority Trial

The aim of the study:
To determine whether treatment with extended-release naltrexone will be as effective as daily buprenorphine hydrochloride with naloxone hydrochloride in maintaining abstinence from heroin and other illicit substances in newly detoxified individuals.
XR-NTX was as effective as BUP-NX treatment as maintaining abstinence from heroin and other illicit substances in opioid dependent patients in a 12 week study.
XR-NTX demonstrated significantly better improvement than BUP-NX on several secondary measures:
- Patients receiving XR-NTX reported significantly less heroin craving and thoughts about heroin than BUP-NX treated patients
- Patient satisfaction with treatment and willingness to recommend to others was significantly higher among XR-NTX patients compared to BUP-NX patients

The safety profiles observed within this study are consistent with the established safety profile of XR-NTX.

- More AE's were reported by XR-NTX than BUP-NX participants (49 vs 25; p < 0.001), but only 10 participants discontinued treatment due to AEs: 4 in the XR-NTX group and 6 in the BUP-NX group
- More withdrawal-related AEs occurred in the XR-NTX group than in the BUP-NX group
- There were no deaths in this study. The one overdose occurred in a BUP-NX treated patient

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Overview of the study:
XR-NTX was as effective as BUP-NX treatment in maintaining patients relapse-free in this 24 week, open-label, multi-site, randomized study (N=570) once patients began study medication (per-protocol population).
In those patients who initiated treatment, several secondary measures were similar for XR-NTX and BUP-NX groups, including number of abstinent days, number of negative urine tests, and reduction in cravings.
- Average opioid craving was initially significantly less for the XR-NTX group than for the BUP-NX group, then converged by week 24
- The safety profile of XR-NTX observed within this 24 week study is consistent with the established safety profile of XR-NTX.
- Other than mild to moderate injection site reactions with XR-NTX, the safety profiles, including fatal and non-fatal overdoses, were similar between groups.
  - Most overdose events occurred in participants who were never inducted or at times distal to last dose of study medication
  - Overdose fatalities occurred in 3 patients treated with BUP-NX and 2 patients treated with XR-NTX.
Pharmacoeconomic Data:

- **Alcohol Dependence.** A published claims database analysis looked at healthcare utilization and costs associated with treatment of alcohol dependence in patients treated with oral naltrexone (n=2064), disulfiram (n=2076), acamprosate (n=5068) and VIVITROL (n=295). Results showed that patients treated with VIVITROL were associated with fewer inpatient detoxification days compared to all other groups, fewer alcoholism-related inpatient days compared to patients receiving disulfiram or acamprosate, and an increase in outpatient substance abuse visits compared to all groups. An economic analysis has been completed assessing the retrospective costs for alcohol dependent commercially insured patients (n=15,502) treated with VIVITROL (n=661), oral naltrexone (n=2391), acamprosate (n=8958) or disulfiram (n=3492), from 2006-2009. VIVITROL was significantly more cost-effective than all three oral medications across all inpatient hospital cost parameters. Underpinning this cost-effectiveness was longer persistence with therapy among VIVITROL-treated patients as compared to other groups and a corresponding pattern of lower rates of admission to inpatient services.

- **Opioid Dependence.** A 6-month retrospective study of insurance claims (n=10,413) assessed total healthcare costs (inpatient + outpatient + pharmacy cost) in patients treated with VIVITROL (n=156), oral naltrexone (n=845), buprenorphine (n=7596) and methadone (n=1916). Results showed the total cost per patient was significantly lower in those using VIVITROL compared to methadone, and no more expensive than buprenorphine or oral naltrexone; due, in large part, to the fact that patients treated with VIVITROL had fewer inpatient admissions compared to all other groups.

- **Pharmacoeconomic data to date derive from retrospective claims analyses rather than prospective randomized trials and therefore use statistical controls such as propensity score matching or instrumental variable analysis for case mix adjustment. Limitations may therefore involve unobserved group differences as well as being limited to six months durations and lacking data about substance use behavior, adverse events and non-health costs.**

Adverse Events:

- More than 1100 patients received VIVITROL in pre-approval trials; approximately 700 patients for >6 months, and 400 patients for >1 year.

- The most common adverse events with VIVITROL for alcohol dependence include nausea, vomiting, injection site reactions (including induration, pruritus, nodules and swelling), muscle cramps, dizziness, fatigue, anorexia, decreased appetite or other appetite disorders. In controlled trials of >6 months in alcohol-dependent patients, 9% patients treated with VIVITROL discontinued treatment due to an adverse event, compared to 7% patients treated with placebo.

- The most common adverse events with VIVITROL for opioid dependence include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. In a controlled trial of 6 months, 2% patients treated with VIVITROL discontinued due to an adverse event, compared to 2% with placebo.

- Serious adverse reactions that may be associated with VIVITROL clinical use include: severe injection site reactions, eosinophilic pneumonia, serious allergic reactions, unintended precipitation of opioid withdrawal, accidental opioid overdose, and depression and suicidality.

**IMPORTANT SAFETY INFORMATION**

After opioid detoxification, patients are likely to have reduced tolerance to opioids. Use of opioids after VIVITROL is discontinued, at the end of a dosing interval or after missing a dose, could result in life-threatening opioid intoxication. Attempts to overcome the opioid blockade while on VIVITROL may result in a fatal overdose. Some people on VIVITROL treatment have had severe reactions at the site of injection (injection site reactions), including tissue death (necrosis). Some of these injection site reactions have required surgery. Patients should be opioid free for a minimum of 7-10 days before starting VIVITROL to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization.

Please see full Prescribing Information for complete safety information, including Contraindications, Warnings and Precautions including: Vulnerability to Opioid Overdose, Injection Site Reactions, Precipitation of Opioid Withdrawal, Hepatotoxicity, Depression and Suicidality, When Reversal of VIVITROL Blockade is Required for Pain Management, Eosinophilic Pneumonia, Hypersensitivity Reactions Including Anaphylaxis, Intramuscular Injections, Alcohol Withdrawal, Interference with Laboratory Tests.

References: