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Testimony subject and nature of testimony Vivitrol has

This request is denied for testimony during the 5/17/19 meeting of the Pharmacy and Therapeutics committee.

VIVITROL® (naltrexone for extended-release injectable suspension)

(See full Prescribing Information at www.VIVITROL.com)

Hello, my name is Dr.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]:

- *Opioid Dependence:* VIVITROL contains naltrexone, an opioid antagonist, and is indicated for the 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

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 in preventing relapse in opioid use disorder (OUD). 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 opioid use disorder.[2] Note that the ASAM guidelines utilize the DSM-5 term "opioid use disorder" whereas VIVITROL is indicated for the DSM-4 term "opioid dependence"[1,2]
- SAMHSA- Government protocol offers recommendations for medications for OUD. OUD medications should be available to patients across all settings and at all levels of care. All patients considering treatment should be educated about effectiveness, risks, and benefits of each of the 3 OUD medications (methadone, buprenorphine, and naltrexone), as well as non-medication options. No data indicate which patients will respond better to which OUD medications. OUD medication decisions should be tailored to the individual patient[3]

Place in Therapy: *Medications from different pharmacologic classes are available for treatment of OUD.*[4]

- 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[1]
- Opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free for a minimum of 7-10 days prior to VIVITROL administration to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization[1]
- VIVITROL requires opioid detoxification prior to use. In patients physically dependent on opioids, VIVITROL will precipitate acute withdrawal when administered[1]
- VIVITROL is not associated with development of tolerance or dependence[1]
- VIVITROL is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or alcohol ingestion[1]
- There is no withdrawal syndrome associated with discontinuation of VIVITROL[2]

Dosing:

- VIVITROL 380mg I.M. (gluteal) is administered every 4 weeks by a healthcare professional using the provided carton components.[1]

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

- *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.[1]

Additional Clinical Studies:

- The Effectiveness of Injectable Extended-Release Naltrexone (XR-NTX) vs. Daily Buprenorphine-Naloxone (BUP-NX) for Opioid Dependence: A Randomized Non-Inferiority Trial[5]

  This was a 12-week, multicenter, outpatient, open-label, randomized clinical trial of 232 opioid-dependent (DSM-IV criteria) individuals, to determine whether treatment with XR-NTX will be as effective as daily BUP-NX in maintaining short-term abstinence from heroin and other illicit substances in newly detoxified individuals. The results showed that XR-NTX was as effective as BUP-NX treatment in maintaining short-term abstinence from heroin and other illicit opioids in opioid dependent participants. On several secondary measures, participants receiving XR-NTX reported less craving and thoughts about heroin, and higher patient satisfaction with treatment compared to BUP-NX.

  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, 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 AE's occurred in the XR-NTX group than in the BUP-NX group. There were no deaths reported in this study and 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[6]

  This was a 24 week, open-label, randomized controlled, comparative effectiveness trial of 570 participants with opioid use disorder (DSM-5 criteria) and had used non-prescribed opioids in the past 30-days, and they began treatment in the community-based inpatient services and were followed up as outpatients. Results showed that XR-NTX was as effective as BUP-NX treatment in maintaining patients relapse-free, once participants began study medication (per-protocol population). Among participants successfully inducted, 24 week relapse events were similar across study groups. Opioid-negative urine samples and opioid-abstinent days favored BUP-NX compared with XR-NTX among the intention-to-treat population but were similar across study groups among the per-protocol populations. Self-reported opioid craving was initially less with XR-NTX then BUP-NX, then converged by week 24. With the exception of mild-to-moderate XR-NTX injection site reactions, treatment-emergent adverse events including overdose did not differ between treatment groups. Overdose fatalities occurred in 3 participants treated with BUP-NX and 2 participants treated with XR-NTX.
- A randomized trial comparing extended-release injectable suspension and oral naltrexone, both combined with behavioral therapy, for the treatment of opioid use disorder[7]

  This was a 24 week, randomized, parallel-group, open-label, pilot clinical trial of 60 opioid-dependent adults who completed inpatient opioid withdrawal and were transitioned to oral NTX. They were stratified by severity of opioid use (six or fewer bags versus more than six bags of heroin per day) and randomly assigned (1:1) to continue treatment with oral NTX (50 mg) or XR-NTX. All participants received weekly behavioral therapy to support treatment and adherence to NTX. Results showed that significantly more patients were retained in treatment for 6 months in the XR-NTX group (57.1%) than in the oral NTX group (28.1%). These results support the use of XR-NTX combined with behavioral therapy as an effective treatment for patients seeking opioid withdrawal and non-agonist treatment for preventing relapse to opioid use disorder.

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Pharmacoeconomic Data:

- *Opioid Dependence:* A 12-month retrospective cohort analysis of insurance claims (n= 29,235) assessing healthcare resource utilization, costs (inpatient, emergency department, outpatient and pharmacy) and in patients treated with extended-release injectable naltrexone (n= 1,041), buprenorphine (n= 20,566), methadone (n= 745), and non-pharmacologic treatment (n=6,883) was conducted. Results showed overall, there was no significant change in total healthcare costs for the extended-release injectable naltrexone group, whereas the costs increased significantly for other groups (buprenorphine= +43%, methadone= +47.7%, non-pharmacologic treatment= +38.8%). This analysis suggests there may be economic value in the use of extended-release injectable naltrexone for OUD.[8]

Adverse Events[1]:

- More than 1100 patients received VIVITROL in pre-approval trials; approximately 700 patients for >6 months, and 400 patients for ≥1year.
- 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.
- Clinically significant adverse reactions that may be associated with VIVITROL use include: accidental opioid overdose, injection site reactions, precipitated opioid withdrawal, hepatotoxicity, depression and suicidality, eosinophilic pneumonia, and hypersensitivity reactions.

Important Safety Information[1]

- Vulnerability to Opioid Overdose: Following VIVITROL treatment opioid tolerance is reduced from pretreatment baseline, and patients are vulnerable to potentially fatal overdose at the end of a dosing interval, after missing a dose, or after discontinuing VIVITROL treatment. Attempts to overcome blockade may also lead to fatal overdose
- Injection Site Reactions: In some cases, injection site reactions may be very severe. Some cases of injection site reactions required surgical intervention
- Precipitation of Opioid Withdrawal: Opioid-dependent and opioid-using patients, including those being treated for alcohol dependence, should be opioid-free before starting VIVITROL treatment, and should notify healthcare providers of any recent opioid use. An opioid-free duration of a minimum of 7-10 days is recommended for patients to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization
- Hepatotoxicity: Cases of hepatitis and clinically significant liver dysfunction were observed in association with VIVITROL treatment during the clinical development program and in the postmarketing period. Discontinue use of VIVITROL in the event of symptoms or signs of acute hepatitis
- Depression and Suicidality: Monitor patients for the development of depression or suicidal thinking
- When Reversal of VIVITROL Blockade Is Required for Pain Management: In an emergency situation in patients receiving VIVITROL, suggestions for pain management include regional analgesia or use of non-opioid analgesics

For the complete safety and additional information, please see the full Prescribing Information for VIVITROL® (naltrexone for extended-release injectable suspension).

References:

1. VIVITROL® (prescribing information). Waltham, MA: Alkermes, Inc., 2018.
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