Commonwealth of Massachusetts Section 35 Commission Meeting

Expert Panel Presentation on Detoxification and Induction on MAT

Presenter: Maria Sullivan, MD, PhD.
Senior Medical Director, Clinical Research and Development, Alkermes Inc.

November 5, 2018
## Extended-release injectable naltrexone

<table>
<thead>
<tr>
<th>Therapeutic use in opioid dependence</th>
<th>Prevention of relapse to opioid dependence, following opioid detoxification&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology</td>
<td>Opioid receptor antagonist&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Dosage and Administration
- The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month.
- The injection should be administered by a healthcare provider as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection, using the carton components provided.

### Clinical considerations
- The administration of VIVITROL is not associated with the development of tolerance or dependence<sup>1</sup>
- Should only be used in patients who are opioid-free for a minimum of 7-10 days<sup>1</sup>
- Monthly injection<sup>1</sup>
- Please see important safety information at end of slide deck<sup>1</sup>

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Induction onto XR-Naltrexone

*Induction* is the process of initial dosing with a medication for OUD treatment until the patient reaches a state of stability, also called initiation onto XR-NTX.

- Induction onto XR-NTX, VIVITROL® (naltrexone for extended-release injectable suspension) remains a challenge for many clinicians.

  - Prior to initiating VIVITROL, 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.

- Clinical studies have evaluated various protocols for induction onto XR-NTX, in both inpatient and outpatient settings; success rates range 33-72%.

  - "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."
Historical Overview of Induction Strategies


BUP, buprenorphine; NTX, naltrexone; OUD, opioid use disorder; XR-NTX, extended-release naltrexone

1. Oral NTX used to prevent relapse after medically supervised withdrawal
2. Clonidine recognized as adjunct in treatment of withdrawal
3. Oral NTX plus clonidine used for “rapid” medically supervised withdrawal
4. Oral NTX, clonidine, and BUP used for medically supervised withdrawal
5. Very-low-dose oral NTX combined with agonists for induction onto early XR-NTX
6. XR-NTX (VIVITROL) approved for OUD
7. Alkermes examined use of ascending doses of oral NTX/placebo plus BUP and ancillary medications for induction onto XR-NTX.
Overview of Medically Supervised Withdrawal and XR-NTX Induction

The available scientific and clinical evidence suggest that there is no single best detoxification method but rather a set of pharmacologic approaches and treatment settings that can be customized to individual patient needs\(^1\)

- Can be safely and effectively accomplished in both inpatient and outpatient settings

Strategies for medically supervised withdrawal prior to induction onto XR-NTX:

- **Gradual opioid agonist taper\(^1\)**
  - (+ancillary medications)

- **Low-dose oral NTX\(^2-6\)**
  - (+ancillary medications; ± BUP)

- **Non-opioid ancillary medications\(^7-10\)**
  - (± benzodiazepine)

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BUP, Buprenorphine; NTX, Naltrexone; XR-NTX, Extended-release injectable naltrexone


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Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine

Maria A. Sullivan, Adam Bisaga, Martina Pavlicova, C. Jean Choi, Kaitlyn Mishlen, Kenneth M. Carpenter, Frances R. Levin, Elias Dakwar, John J. Mariani, Edward V. Nunes

Oral NTX- vs BUP-assisted Induction Onto XR-NTX
Aims and Study Design

A randomized trial in participants seeking treatment for heroin or prescription opioid dependence, to compare XR-NTX outpatient induction rates between two methods of opioid withdrawal management.

<table>
<thead>
<tr>
<th>Opioid Dependence*</th>
<th>Low Use</th>
<th>High Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, 150 (100%)</td>
<td>71 (47%)</td>
<td>79 (53%)</td>
</tr>
</tbody>
</table>

Patient Population
• 18–60 years old with current opioid dependence (DSM-IV) ≥6 months
• Stratified by severity of opioid dependence*

N = 150
2:1

Transition Period
Days 1–8

Oral NTX-assisted induction

Monthly XR-NTX Injections

1st injection

2nd injection

Transition Period
Days 1–15

BUP-assisted induction

*Low use (≤5 bags (~10 mg) of heroin or ≤200 mg of morphine equivalents per day) and high use (>5 bags of heroin or >200 mg of morphine equivalents per day)
BUP, buprenorphine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; NTX, naltrexone; XR-NTX, extended-release naltrexone
Oral NTX- vs BUP-assisted Induction Onto XR-NTX
Dosing Regimen During Transition Period

<table>
<thead>
<tr>
<th></th>
<th>Day 1/2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral NTX-assisted</td>
<td>BUP 2 mg</td>
<td>Washout</td>
<td>NTX 1 mg</td>
<td>NTX 3 mg</td>
<td>NTX 12 mg</td>
<td>NTX 25 mg</td>
<td>XR-NTX: 380 mg IM</td>
<td>--</td>
</tr>
<tr>
<td>induction</td>
<td>sublingually every 1-2 hrs, up to 8 mg</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUP-assisted</td>
<td>BUP 6 mg</td>
<td>BUP 4 mg</td>
<td>BUP 4 mg</td>
<td>BUP 2 mg</td>
<td>BUP 1 mg</td>
<td>--</td>
<td>XR-NTX: 380 mg IM</td>
<td></td>
</tr>
<tr>
<td>induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ancillary</td>
<td>clonidine, clonazepam, prochlorperazine, trazodone, zolpidem as needed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medications*</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

* Ancillary medications offered included clonidine (0.1 mg q.i.d., plus every 4 hours as needed; maximum daily dose, 1.2 mg), clonazepam (0.5mg q.i.d.; maximum daily dose, 2.0 mg), prochlorperazine (10 mg t.i.d.), trazodone(100 mg h.s.), and zolpidem (10 mg h.s.).

qid, 4 times daily; tid, three times daily; hs, at bedtime
BUP, buprenorphine; NTX, naltrexone; XR-NTX, extended-release naltrexone
Withdrawal severity and treatment dropout during the induction period were comparable in the two treatment arms during the first 7 days of treatment.

Participants were significantly more likely to successfully initiate XR-NTX after a rapid 8-day oral NTX-assisted induction than after a standard 15-day BUP induction.
Study limitations include: the study was non-blinded, and patients received more care than in typical practice.
Outpatient Transition to Extended-Release Injectable Naltrexone for Patients With Opioid Use Disorder: A Phase 3 Randomized Trial

Adam Bisaga, Paolo Mannelli, Miao Yu, Narinder Nangia, Christine E. Graham, D. Andrew Tompkins, Thomas R. Kosten, Sarah C. Akerman, Bernard L. Silverman, Maria A. Sullivan


Tompkins DA et al. Poster presented at the ASAM Annual Conference; April 12–15, 2018; San Diego, USA. Poster 33

Financial support for the conduct of the research and preparation of this article was provided by Alkermes, Inc.
Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX

**Aim and Study Design**

- Phase 3, multicenter, randomized, double-blind, PBO controlled study to examine safety and efficacy of low-dose oral NTX, combined with BUP and standing ancillary medications, to transition patients with OUD onto XR-NTX

<table>
<thead>
<tr>
<th>Opioid Dependence*</th>
<th>Prescription Opioid</th>
<th>Heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, 378 (100%)</td>
<td>136 (36%)</td>
<td>242 (64%)</td>
</tr>
</tbody>
</table>

**Transition Period**
- Days 1–8
  - NTX/BUP
  - NTX/PBO-B
  - PBO-N/PBO-B

**Monthly XR-NTX Injections**
- 1st injection (primary study endpoint)
- 2nd injection
- 3rd injection

**Patient Population**
- 18–60 years of age with moderate/severe OUD (DSM-5)
- Self-reported current opioid use + UDT
- ≥ Mild withdrawal symptoms

*Baseline patient characteristics were similar across transition-protocol groups
†Primary endpoint: The proportion of patients who received and tolerated a XR-NTX injection
BUP, buprenorphine; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; NTX, naltrexone; OUD, opioid use disorder; PBO-B, placebo for buprenorphine; PBO-N, placebo for naltrexone; UDT, urine drug test; XR-NTX, extended-release naltrexone


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**Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX Dosing Regimen During Transition Period**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st and 2nd Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTX or PBO-N</td>
<td>0.25 mg</td>
<td>0.25 mg</td>
<td>0.5 mg</td>
<td>1.5 mg</td>
<td>3 mg</td>
<td>7.5 mg</td>
<td>15 mg</td>
<td>XR-NTX: 380 mg IM</td>
</tr>
<tr>
<td>BUP or PBO-B</td>
<td>2 mg + 2 mg†</td>
<td>2 mg</td>
<td>2 mg</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Standing Ancillary Medications*</td>
<td></td>
<td></td>
<td></td>
<td>fixed doses of clonidine, clonazepam, trazodone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Standing ancillary medications included fixed doses of clonidine (0.1 mg tid), clonazepam (0.5 mg tid), trazodone (100 mg qhs)
2nd dose administered ≥1h after 1st dose; †Optional 2 mg buprenorphine at home
BUP, buprenorphine; NTX, naltrexone; PBO-B, placebo for buprenorphine; PBO-N, placebo for naltrexone
**Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX**

**Successful Induction onto XR-NTX**

- Transition to XR-NTX was similar regardless of transition protocol ($P > .383$)
  - Primary study endpoint was not met
- Prescription opioid users were more likely to transition to XR-NTX than heroin users ($P = .0004$)
- Majority (57.3%) who passed naloxone challenge and received XR-NTX had opioid-positive UDT on day of induction

*Tolerance was demonstrated by mild withdrawal scores with COWS score $\leq 12$ or SOWS score $\leq 10$.  
BUP, buprenorphine; NTX, naltrexone; PBO-B, placebo for buprenorphine; PBO-N, placebo for naltrexone; XR-NTX, extended-release naltrexone; UDT, urine drug test  
Changes in COWS and SOWS were similar. Overall withdrawal scores were mild to moderate during the transition period. Craving scores declined steadily.
Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX Withdrawal and Craving Scores

Study limitations include: frequency and duration of study visits exceeded those common in outpatient practice, generalizability to real-world patient populations may be limited, and doses of oral naltrexone used in the study are not commercially available or FDA approved.
Baseline prescription opioid use, non IV drug use, and VAS score <80† were significantly associated with successful induction onto XR-NTX.
Study limitations include: this was a post hoc analysis and the parent study evaluated a 7-day outpatient regimen with standing ancillary medications; therefore the findings may not be generalizable to other protocols or settings.
# Safety Analysis

Most AEs were mild to moderate in severity

- In addition, in a poster presentation most common TEAEs presented were: diarrhea (5.8%), anxiety (5.0%), nausea (4.0%)

- Four patients (1.1%) discontinued study due to AE

- No overdoses or deaths occurred during the study

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## Table: Treatment-Emergent Adverse Events (TEAEs) by Category and Severity

<table>
<thead>
<tr>
<th>Category</th>
<th>NTX/BUP (N = 126)</th>
<th>NTX/PBO-B (N = 126)</th>
<th>PBO-N/PBO-B (N = 126)</th>
<th>Total (N = 378)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>44 (34.9)</td>
<td>31 (24.6)</td>
<td>48 (38.1)</td>
<td>123 (32.5)</td>
</tr>
<tr>
<td>TEAE by severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>23 (18.3)</td>
<td>12 (9.5)</td>
<td>15 (11.9)</td>
<td>50 (13.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>17 (13.5)</td>
<td>13 (10.3)</td>
<td>25 (19.8)</td>
<td>55 (14.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>4 (3.2)</td>
<td>6 (4.8)</td>
<td>8 (6.3)</td>
<td>18 (4.8)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>1 (0.8)</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Any SADR</td>
<td>0</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

AE, adverse event; BUP, buprenorphine; NTX, naltrexone; PBO-B, placebo for buprenorphine; PBO-N, placebo for naltrexone; SADR, serious adverse drug reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Bisaga A et al. Drug Alcohol Depend. 2018;187:171-178; Bisaga A et al. Poster presented at the AAAP Annual Meeting; December 7-10, 2018; San Diego, USA.
### Induction Strategy: Non-opioid, Benzodiazepine-free Protocols

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>Krupitsky et al. 2017¹</td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Rudolf et al. 2018²</td>
</tr>
<tr>
<td>Tizanidine</td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Gorodetsky et al. 2017³</td>
</tr>
<tr>
<td>Lofexidine</td>
<td></td>
</tr>
</tbody>
</table>

These studies have proposed non-opioid, non-benzodiazepine regimens¹-³

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The available scientific and clinical evidence suggest that there is no single best detoxification method but rather a set of pharmacologic approaches and treatment settings that can be customized to individual patient needs. A component of successful induction onto XR-NTX may be medical management of withdrawal with ancillary medications.

Strategies for medically supervised withdrawal prior to induction onto XR-NTX:

- Gradual opioid agonist taper (± ancillary medications)
- Low-dose oral NTX (± ancillary medications; ± BUP)
- Non-opioid ancillary medications (± benzodiazepine)

BUP, Buprenorphine; NTX, Naltrexone; XR-NTX, Extended-release injectable naltrexone; HCP, healthcare provider

VIVITROL®
(naltrexone for extended-release injectable suspension)

Product Safety Information

For complete prescribing information please visit
https://www.vivitrol.com/content/pdfs/prescribing-information.pdf
VIVITROL®
(naltrexone for extended-release injectable suspension)

- VIVITROL is indicated for the 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

- VIVITROL is indicated for the prevention of relapse to opioid dependence, following opioid detoxification
  - Opioid-dependent patients and opioid-using patients, including those being treated for alcohol dependence, should be opioid-free for a minimum of 7–10 days before starting VIVITROL

- Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support
Contraindications

- Patients receiving opioid analgesics
- Patients with current physiologic opioid dependence
- Patients in acute opioid withdrawal
- Any individual who has failed the nalaxone challenge test or has a positive urine screen for opioids
- Patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of diluent
Warnings and Precautions

- Vulnerability to opioid overdose
- Injection site reactions
- Unintended precipitation of opioid withdrawal
- Hepatotoxicity
- Depression and suicidality
- When reversal of VIVITROL blockade is required for pain management

- Eosinophilic pneumonia
- Hypersensitivity reactions
- Intramuscular injections
- Alcohol withdrawal
- Interference with laboratory tests

Warnings and Precautions
Vulnerability to Opioid Overdose: Reduced Tolerance

- Reduced tolerance to opioids after detox
  - VIVITROL blockade of exogenous opioids wanes and eventually dissipates
    - VIVITROL-treated patients may respond to lower doses of opioids than previously used
    - Previously tolerated opioid doses could be life-threatening
    - Fatal outcomes reported in patients who used opioids
      - at the end of a dosing interval
      - after missing a scheduled dose
      - after discontinuing treatment

Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after VIVITROL treatment is discontinued

Family members and caregivers should be alerted to this important information

Attempts to overcome the opioid blockade effect of VIVITROL

- Blockade effect of VIVITROL to exogenous opioids is surmountable
- Potential risk to patients who attempt to overcome blockade by administering large amounts of exogenous opioids
- Any attempt by a patient to overcome the antagonism by taking opioids is especially dangerous and may lead to life-threatening opioid intoxication or fatal overdose

Patients should be told of the serious consequences of trying to overcome the opioid blockade
Warnings and Precautions
Injection Site Reactions

- VIVITROL injections may be followed by:
  - pain, tenderness, induration, swelling, erythema, bruising, pruritus
  - some injection site reactions may be very severe
- Additional cases of injection site reactions in postmarketing period:
  - induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis

Patients should be informed that any concerning injection site reactions should be brought to attention of the healthcare provider.

Patients exhibiting signs of abscess, cellulitis, necrosis, or extensive swelling should be evaluated by a physician to determine if referral to a surgeon is warranted.
Opioid-dependent patients, including those treated for alcohol dependence should be opioid free (including tramadol) for a minimum of 7-10 days before starting VIVITROL treatment
- to prevent occurrence of precipitated withdrawal in patients dependent on opioids, or exacerbation of a preexisting subclinical abstinence syndrome
- patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as two weeks

Patients may experience precipitated withdrawal despite having a negative urine toxicology screen or tolerating a naloxone challenge test

Patients treated for alcohol dependence with VIVITROL should be assessed for underlying opioid dependence and for any recent use of opioids prior to initiation of treatment with VIVITROL

Patients necessitating a more rapid transition from agonist to antagonist therapy should be closely monitored in an appropriate medical setting where precipitated withdrawal can be managed

Healthcare providers should always be prepared to manage withdrawal symptomatically with non-opioid medications
Warnings and Precautions
Hepatotoxicity

- Cases of hepatitis and clinically significant liver dysfunction were observed in association with VIVITROL exposure during the clinical development program and in the postmarketing period.
-Transient, asymptomatic hepatic transaminase elevations were also observed
  - potential causative or contributory etiologies
    - pre-existing alcoholic liver disease
    - hepatitis B and/or C infection
    - concomitant usage of other potentially hepatotoxic drugs

Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis

Use of VIVITROL should be discontinued in the event of symptoms and/or signs of acute hepatitis

Warnings and Precautions
Depression and Suicidality

- Opioid- and alcohol-dependent individuals, including those taking VIVITROL, should be monitored for the development of depression or suicidal thinking.
- Families and caregivers of patients being treated with VIVITROL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient’s healthcare provider.

Alcohol Dependence
- Controlled clinical trials: adverse events of a suicidal nature were infrequent overall, but were more common in patients treated with VIVITROL than in placebo treated patients (1% vs 0).
- 24-week, placebo-controlled pivotal trial: adverse events involving depressed mood were reported by 10% of patients treated with VIVITROL 380 mg as compared to 5% of patients treated with placebo injections.

Opioid Dependence
- Open-label, long-term safety study: adverse events of a suicidal nature were reported by 5% of opioid-dependent patients treated with VIVITROL 380 mg and 10% of opioid-dependent patients treated with oral naltrexone.
- 24-week, placebo-controlled pivotal trial: adverse events involving depressed mood or suicidal thinking were not reported by any patient in either treatment group (VIVITROL 380 mg or placebo).

Warnings and Precautions
Reversal of VIVITROL Blockade for Pain Management

In an emergency situation involving patients receiving VIVITROL, suggestions for pain management include:
- regional analgesia
- non-opioid analgesics

If opioid therapy is required as part of anesthesia or analgesia
- patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of a surgical or diagnostic procedure
- opioid therapy must be administered by individuals specifically trained in the use of anesthetic drugs and the management of respiratory effects of potent opioids
  - specifically, establishment and maintenance of a patent airway and assisted ventilation

Irrespective of the drug chosen to reverse VIVITROL blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Eosinophilic pneumonia

- Clinical trials: one diagnosed case, one suspected case:
  - Both cases required hospitalizations, and resolved after treatment with antibiotics and corticosteroids
  - Similar cases reported in postmarketing use
- Diagnosis should be considered if patients develop progressive dyspnea and hypoxemia

Patients should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia.

Clinicians should consider the possibility of eosinophilic pneumonia in patients who do not respond to antibiotics.
Hypersensitivity reactions (including anaphylaxis)

- Cases of urticaria, angioedema, and anaphylaxis have been observed with use of VIVITROL in the clinical trial setting and 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.
Warnings and Precautions
Intramuscular Injections, Alcohol Withdrawal, Interference with Laboratory Tests

**Intramuscular injections**
- As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder (e.g., hemophilia and severe hepatic failure)

**Alcohol withdrawal**
- Use of VIVITROL does not eliminate or diminish alcohol withdrawal symptoms

**Interference with laboratory tests**
- VIVITROL may be cross-reactive with certain immunoassay methods for the detection of drugs of abuse (especially opioids) in urine
- For further information, reference to the specific immunoassay instructions is recommended
Most Frequent Adverse Reactions

**Alcohol Dependence**
(occurring in ≥5%)

- 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

**Opioid Dependence**
(occurring in ≥2%)

- hepatic enzyme abnormalities
- injection site pain
- nasopharyngitis
- insomnia
- toothache
Possible Serious Adverse Reactions

- Severe injection site reactions
- Eosinophilic pneumonia
- Serious allergic reactions
- Unintended precipitation of opioid withdrawal
- Accidental overdose
- Depression and suicidality