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

The year 2017 marked a milestone for research on the treatment of opioid dependence. For the first time, clinical trial data became available regarding the comparative effectiveness of buprenorphine-naloxone and extended-release naltrexone. This newsletter reviews an open-label study (known as X:BOT) published by Lee and colleagues in The Lancet and an open-label study published by Tanum and colleagues in JAMA Psychiatry. This overview also includes commentary from members of the Meeting the Need Steering Committee.

The X:BOT study evaluated patients with opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5), criteria. VIVITROL® (naltrexone for extended-release injectable suspension) was approved based on Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR), criteria for opioid dependence.

Please see Important Safety Information for VIVITROL throughout this newsletter. For additional Important Safety Information about VIVITROL, please see Brief Summary of Prescribing Information on page 11 and back cover.
Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicenter, open-label, randomized controlled trial.\(^1\)


**Design**

This US study, called X:BOT, was a 24-week, multicenter, open-label, randomized clinical trial of adult (age ≥18 years) outpatients with opioid use disorder (DSM-5 criteria). It was designed to compare the effectiveness of extended-release naltrexone (XR-NTX) versus sublingual buprenorphine-naloxone (BUP-NX) for the prevention of relapse. The National Institute on Drug Abuse (NIDA) Clinical Trials Network sponsored the study. The authors and the study sponsor designed and implemented the study, collected and analyzed the data, wrote the initial manuscript draft, and were responsible for data integrity. Indivior PLC donated BUP-NX and had access to periodic safety data only, with no input on or review of this manuscript. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

A total of 772 participants were recruited and screened during voluntary, usual-care, inpatient detoxification admissions. All eligible subjects had used non-prescribed opioids in the previous 30 days. A total of 570 participants were randomized to receive either daily sublingual self-administered BUP-NX 8 mg/day to 24 mg/day (n=287) or XR-NTX 380 mg administered intramuscularly every fourth week (n=283) (Figure 1).

**Figure 1.** Study Design and Patient Population

**STUDY DESIGN**

- 772 Screened for Eligibility
- 570 Randomized\(^*\)

202 individuals were excluded because they dropped out of treatment, did not meet eligibility criteria, completed screening but were not eligible, or other reasons.

**Intent-to-Treat**

- 283 XR-NTX
- 204 BUP-NX

**Per-Protocol**

- 180 mg/4 wks
- 8-24 mg/d
- 96 Completed
- 115 Completed

Participants who were randomized but unable to initiate treatment were considered induction failures and excluded from the per-protocol population.

\(^*\)277 randomized early; 353 randomized late.

BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone.

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**IMPORTANT SAFETY INFORMATION**

**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.

Please see important safety information for VIVITROL throughout this newsletter. For additional important safety information about VIVITROL, please see brief summary of prescribing information on page 11 and back cover.
Participants assigned to early randomization were randomized within 72 hours of last opioid use, including opioids used for detoxification. Participants randomized more than 72 hours after last opioid use were included in the late-randomization group.

XR-NTX treatment could be initiated at least 3 days from the patient’s last opioid use, an opioid-negative urine drug test (UDT), and a negative naloxone challenge. These criteria were not met by 79 participants. BUP-NX treatment could be initiated once withdrawal symptoms emerged. This criterion was not met by 17 participants.

Additional exclusion criteria included the presence of serious medical, psychiatric, or substance use disorders; liver function tests greater than 5 times the upper limit of normal; suicidal or homicidal state; allergy or sensitivity to XR-NTX or BUP-NX; and inability to have safe intramuscular XR-NTX treatment. Women who were or could become pregnant or were breastfeeding were also excluded.

The intention-to-treat (ITT) population included all randomized participants. The per-protocol population included only the participants who began study medication.

ENDPOINTS

The primary endpoint was time to relapse. Relapse was defined as opioid use after Day 20—either 4 consecutive weeks with at least 1 day of non-study opioid as measured by a weekly UDT or 7 consecutive days with self-reported opioid use. Secondary endpoints reported in this publication included the proportion of participants initiated onto study medication, safety, frequency of non-study opioid use, and opioid craving. Other secondary outcomes evaluated in this study were not reported in the publication.

Results

Demographic data for the 570 randomized patients are shown in Table 1. The population was about 70% male and about 75% white and had about 12 years of opioid use on average.

For XR-NTX, treatment was initiated in 53% of participants (n=57) in the early randomization group and 84% of participants (n=148) in the late-randomization group.

Table 1. Demographics and Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intention to Treat (N=570)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extended-release Naltrexone (n=283)</td>
</tr>
<tr>
<td>Age, years</td>
<td>34.0 (9.5)</td>
</tr>
<tr>
<td>Male</td>
<td>69%</td>
</tr>
<tr>
<td>Female</td>
<td>31%</td>
</tr>
<tr>
<td>White</td>
<td>73%</td>
</tr>
<tr>
<td>Opioid use, years</td>
<td>12.8 (9.0)</td>
</tr>
<tr>
<td>Opioid used in the 7 days before detox admission</td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>81%</td>
</tr>
<tr>
<td>Opioid analgesic</td>
<td>15%</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>2%</td>
</tr>
<tr>
<td>Methadone</td>
<td>1%</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont.)

Vulnerability to Opioid Overdose (cont.):

- 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.
Relapse (primary endpoint) in the ITT population

In the ITT population, opioid-relapse events occurred in 65% of XR-NTX–treated patients and in 57% of BUP-NX–treated patients (odds ratio [OR], 1.44; 95% confidence interval [CI], 1.02 to 2.01; P=0.036; Figure 2), mainly because many randomized participants in the ITT population did not initiate treatment with XR-NTX. Study sites varied in detoxification protocols and length of inpatient stay. Protocols included no opioids, 3- to 5-day methadone tapers, and 3- to 14-day buprenorphine tapers.

In this ITT population, the median time to relapse was 8.4 weeks in the XR-NTX group and 14.4 weeks in the BUP-NX group (hazard ratio [HR], 1.36; 95% CI, 1.10 to 1.68; P=0.004).

Relapse (primary endpoint) in the per-protocol population

In the per-protocol population, relapse events occurred in 52% of XR-NTX–treated patients and in 56% of BUP-NX–treated patients (Figure 3). The difference in relapse events in the per-protocol versus ITT populations was accounted for largely by a high incidence of early relapse due to XR-NTX induction failures.

The median time to relapse in this per-protocol population was 20.4 weeks in the XR-NTX group and 15.2 weeks in the BUP-NX group (HR, 0.92; 95% CI, 0.71 to 1.18; P=0.49).

In this per-protocol population, 47% of patients inducted to XR-NTX (96/204) and 43% of patients inducted to BUP-NX (115/270) completed 24 weeks of treatment (did not end medication early).

Figure 2. Opioid Relapse (Weeks 3-24) in the ITT Population

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX</th>
<th>BUP-NX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>65%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Figure 3. Opioid Relapse (Weeks 3-24) in the Per-Protocol Population

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX</th>
<th>BUP-NX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>52%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Odds ratio, 1.44; 95% confidence interval, 1.02 to 2.01; P<0.036.
BUP-NX, buprenorphine-naloxone; ITT, intention-to-treat; XR-NTX, extended-release naltrexone.

Commentary from the Steering Committee

Q: What are some of the unanswered questions about these studies?

Dr. Jeffrey Berman: One question is: What specific psychosocial interventions were provided? Psychosocial therapy is an important part of treatment.

Dr. Laura Leahy: One of the things that may not be clear to some readers of these articles is the fact that extended-release naltrexone is not an opioid. Healthcare providers should clearly communicate this when reviewing treatment options with patients and caregivers.

Linda Frazier: These studies indicated that extended-release naltrexone and buprenorphine-naloxone can both be effective medicines. However, how do providers identify who is right for which treatment?

Dr. Genie Bailey: Also what role does patient preference play in treatment outcomes?

Dr. Paolo Mannelli: I have questions about the detoxification protocols. There was not a lot of detail about the detoxification protocols used, and the protocols varied. [For more information on detoxification, refer to the VIVITROL question-and-answer page on the Meeting the Need website.]
Secondary endpoint (craving)

Subjective, self-reported opioid craving declined rapidly from baseline in both treatment groups. Opioid craving was initially less with XR-NTX than with BUP-NX ($P=0.0012$) but converged by Week 24 ($P=0.20$) (Figure 4).

Secondary endpoint (safety)

The proportion of participants reporting adverse events and serious adverse events did not differ between treatment groups, with the exception of injection site reactions among XR-NTX-treated patients (see Table 2 on page 6). All of the injection site reactions in the XR-NTX group were of minor to moderate severity. Five fatal overdoses occurred, in 2 participants treated with XR-NTX and in 3 participants treated with BUP-NX.

This is not a complete list of adverse events for VIVITROL. Please see Important Safety Information and Brief Summary of Prescribing Information on page 11 and back cover for additional safety information.
The authors concluded that although it was more difficult to initiate patients onto XR-NTX than onto BUP-NX (which negatively affected overall relapse rates with XR-NTX), both medications were equally safe and effective once initiated. They also noted that these findings of noninferiority align with the results of the Norwegian study by Tanum et al (see page 7).

Study Limitations
Study sites varied in detoxification protocols and length of inpatient stay. Ease of induction is a well-known limitation of XR-NTX compared to BUP-NX. A real-world effectiveness study such as X:BOT includes more sources of bias than a tightly managed efficacy study but potentially has higher generalizability.

### IMPORTANT SAFETY INFORMATION

**WARNINGS AND PRECAUTIONS (cont.)**

**Precipitation of Opioid Withdrawal (cont.):**
- 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.

Please see Important Safety Information for VIVITROL throughout this newsletter.
For additional Important Safety Information about VIVITROL, please see Brief Summary of Prescribing Information on page 11 and back cover.
Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial.²

**Design**

This Norwegian study was a 12-week, multicenter, outpatient, open-label, randomized, clinical noninferiority trial comparing the effectiveness of injectable extended-release naltrexone (XR-NTX) with daily oral buprenorphine-naloxone (BUP-NX) for the treatment of opioid dependence. Because this study was not blinded, participants in each treatment group knew which medication they were receiving.

The study was supported by unrestricted grants from the Research Council of Norway and the Western Norway Regional Health Authority. Financial support was also received from the Norwegian Centre for Addiction Research at the University of Oslo and from Akershus University Hospital. The funding organizations had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Alkermes, Inc., was allowed to comment on the manuscript before submission for publication and supplied XR-NTX for the study.

All patients were 18 years to 60 years of age and met *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.*, criteria for opioid dependence. A total of 232 patients were recruited for the study from outpatient addiction clinics and detoxification units. Patients were excluded if they were pregnant or breastfeeding, had other drug or alcohol dependence, or had serious somatic or psychiatric illness interfering with participation. After screening and inclusion, participants were referred to a detoxification unit and randomized to treatment after detoxification (see Figure 5).

Of the original 232 subjects, 159 were randomized to receive either daily oral flexible-dose BUP-NX 4 mg/day to 24 mg/day (n=79) or XR-NTX 380 mg given intramuscularly every fourth week (n=80). All participants received weekly UDTs and were asked to attend standard drug counseling. However, no behavioral interventions could be initiated.

---

**Figure 5. Study Design and Patient Population**

232 Screened for Eligibility

159 Randomized

73 individuals were excluded due to: refusal to participate (51), not meeting inclusion criteria (9), failing detoxification (6) or other reasons (7).

80 XR-NTX 380 mg

71 Received Treatment

56 Completed

79 BUP-NX 4-24 mg/d

72 Received Treatment

49 Completed

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**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (cont.)**

**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.
 PRIMARY ENDPOINTS

The researchers sought to determine whether XR-NTX was noninferior to BUP-NX via the measurement of 3 primary endpoints: the number of days of use of heroin and other illicit opioids, the trial completion rate, and the proportion of UDTs that were negative for illicit opioids. The weekly UDTs were calculated as the number of opioid-negative urine drug screens divided by the total number of attended tests. For all participants, missing UDTs were considered positive for opioids.

Results

Demographic data for the 159 randomized patients are shown in Table 3. The population was about 70% male and about 90% white and had about 9 years of heavy opioid use on average.

With respect to days of use of heroin and other illicit opioids, treatment with XR-NTX showed noninferiority to BUP-NX. For XR-NTX compared with BUP-NX, the mean difference in days of heroin use was -3.2 (95% CI, -4.9 to -1.5; \( P < 0.001 \)) and the mean difference in days of other illicit opioid use was -2.7 (95% CI, -4.6 to -0.9; \( P < 0.001 \); see Figure 6 on page 9).

<table>
<thead>
<tr>
<th>Table 3. Demographics and Baseline Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention to Treat (N=159)</strong></td>
</tr>
<tr>
<td><strong>Extended-release Naltrexone (n=80)</strong></td>
</tr>
<tr>
<td><strong>Buprenorphine-Naloxone (n=79)</strong></td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>36.4 (8.8)</td>
</tr>
<tr>
<td>35.7 (8.5)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>61 (76.3%)</td>
</tr>
<tr>
<td>54 (68.4%)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>19 (23.6%)</td>
</tr>
<tr>
<td>25 (31.6%)</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>72 (90%)</td>
</tr>
<tr>
<td>70 (88.6%)</td>
</tr>
<tr>
<td>Heavy opioid use, years</td>
</tr>
<tr>
<td>8.9 (7.8)</td>
</tr>
<tr>
<td>9.6 (10.5)</td>
</tr>
<tr>
<td>Heroin use, years</td>
</tr>
<tr>
<td>6.9 (5.8)</td>
</tr>
<tr>
<td>6.7 (5.2)</td>
</tr>
<tr>
<td>Other illicit opioid use, years</td>
</tr>
<tr>
<td>2.4 (5.1)</td>
</tr>
<tr>
<td>3.2 (7.0)</td>
</tr>
<tr>
<td>Heroin use during past 30 days</td>
</tr>
<tr>
<td>7.6 (11.0)</td>
</tr>
<tr>
<td>12.0 (12.9)</td>
</tr>
<tr>
<td>Other illicit opioid use during past 30 days</td>
</tr>
<tr>
<td>8.2 (11.1)</td>
</tr>
<tr>
<td>14.5 (13.2)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) or number (%).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont.)

**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.

Please see Important Safety Information for VIVITROL throughout this newsletter.
For additional Important Safety Information about VIVITROL, please see Brief Summary of Prescribing Information on page 11 and back cover.
XR-NTX also showed noninferiority to BUP-NX with respect to treatment retention at the end of the study. Specifically, the proportion of participants retained in the XR-NTX group (n=71) was noninferior to that in the BUP-NX group (n=72) (difference, -0.1; 95% CI, -0.2 to 0.1; \( P = 0.04 \)). In addition, the percentage of patients who completed the 12 weeks of treatment was 70% (n=56) in the XR-NTX group and 62% (n=49) in the BUP-NX group. The retention time in days is shown in Figure 7.

**Figure 6.** Mean Difference in Opioid Use, XR-NTX vs BUP-NX

-3.2

DAYS USE OF HEROIN

-2.7

DAYS USE OF OTHER ILLICIT OPIOIDS

BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone.

**Figure 7.** Study Retention Time for XR-NTX vs BUP-NX

<table>
<thead>
<tr>
<th>Time (Days)</th>
<th>XR-NTX</th>
<th>BUP-NX</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>69.3</td>
<td>63.7</td>
</tr>
</tbody>
</table>

P=0.33, log-rank test.
BUP-NX, buprenorphine-naloxone; XR-NTX, extended-release naltrexone; SD, standard deviation.

XR-NTX also showed noninferiority to BUP-NX with respect to treatment retention at the end of the study. Specifically, the proportion of participants retained in the XR-NTX group (n=71) was noninferior to that in the BUP-NX group (n=72) (difference, -0.1; 95% CI, -0.2 to 0.1; \( P = 0.04 \)). In addition, the percentage of patients who completed the 12 weeks of treatment was 70% (n=56) in the XR-NTX group and 62% (n=49) in the BUP-NX group. The retention time in days is shown in Figure 7.

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**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (cont.)**

**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.
XR-NTX showed noninferiority to BUP-NX in terms of the total number of opioid-negative UDTs as well. Specifically, treatment with XR-NTX was noninferior to BUP-NX regarding the group proportion of the total number of opioid-negative UDTs (mean [SD], 0.9 [0.3] and 0.8 [0.4], respectively; mean difference, 0.1; 95% CI, -0.04 to 0.2; \( P < 0.001 \); Figure 8).
VIVITROL® (naltrexone for extended-release injectable suspension)

INTRAMUSCULAR


INDICATIONS AND USAGE: 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. In addition, VIVITROL is indicated for the 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, patients with current physiologic opioid dependence, patients in acute opioid withdrawal, any individual who has failed the naltrexone challenge test or has a positive urine screen for opioids, and patients who have previously exhibited hypersensitivity to naltrexone, poly lactide-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 reduced tolerance to opioids. VIVITROL blocks the effects of exogenous opioids for approximately 28 days after administration. However, as the blockade wanes and eventually dissipates completely, patients who have been treated with VIVITROL may respond to lower doses of opioids than previously used, just as they would have shortly after completing detoxification. This could result in potentially life threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.) if the patient uses previously tolerated doses of opioids. 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 should be alerted that they may be more sensitive to opioids, even at lower doses, after VIVITROL treatment is discontinued, especially at the end of a dosing interval (i.e., near the end of the month that VIVITROL was administered), or after a dose of VIVITROL is missed. It is important that patients inform family members and the people closest to the patient of this increased sensitivity to opioids and the risk of overdose. There is also the possibility that a patient who is treated with VIVITROL could overcome the opioid blockade effect of VIVITROL. 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 become tolerant to 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. 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. In the clinical trials, one patient developed an area of induration that continued to enlarge after 4 weeks, with subsequent development of necrotic tissue that required surgical excision. In the postmarketing period, additional cases of injection site reaction with features including induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis, have been reported. Some cases required surgical intervention, including debridement of necrotic tissue. Some cases resulted in significant scarring. The reported cases occurred primarily in female patients. VIVITROL is administered as an intramuscular gluteal injection, and inadvertent subcutaneous injection of VIVITROL may increase the likelihood of severe injection site reactions. The needles provided in the carton are customized needles. VIVITROL must not be injected using any other needle. The needle lengths (either 1 1/2 inches or 2 inches) may not be adequate in every patient because of body habitus. Body habitus should be assessed prior to each injection for each patient to assure that the proper needle is selected and that the needle length is adequate for intramuscular administration. Healthcare professionals should ensure that the VIVITROL injection is given correctly, and should consider alternate treatment for those patients whose body habitus precludes an intramuscular gluteal injection with one of the provided needles. Patients should be informed that any concerning injection site reactions should be brought to the attention of the healthcare professional. 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.

Precipitation of Opioid Withdrawal: The symptoms of spontaneous opioid withdrawal (which are associated with the discontinuation of opioid in a dependent individual) are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Review of postmarketing cases of precipitated opioid withdrawal in association with naltrexone treatment has identified cases with symptoms of withdrawal severe enough to require hospital admission, and in some cases, management in the intensive care unit. To prevent occurrence of precipitated withdrawal in patients dependent on opioids, or exacerbation of a pre-existing subclinical withdrawal syndrome, 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 precipitation of withdrawal symptoms 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. In every case, healthcare providers should always be prepared to manage withdrawal symptomatically with non-opioid medications because there is no completely reliable method for determining whether a patient has had an adequate opioid-free period. A naltrexone challenge test may be helpful; however, a few case reports have indicated that patients may experience precipitated withdrawal despite having a negative urine toxicology screen or tolerating a naltrexone challenge test (usually in the setting of transitioning from buprenorphine treatment). Patients should be made aware of the risks associated with precipitated withdrawal and encouraged to give an accurate account of last opioid use. Patients treated for alcohol dependence with VIVITROL should also be assessed for underlying opioid dependence and for any recent use of opioids prior to initiation of treatment with VIVITROL. Precipitated opioid withdrawal has been observed in alcohol-dependent patients in circumstances where the prescriber had been unaware of the additional use of opioids or co-dependence on opioids. 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 in the clinical trials and postmarketing period. Although patients with clinically significant liver disease were not systematically studied, clinical trials did include patients with asymptomatic viral hepatitis infections. When patients presented with elevated transaminases, there were often other potential causative or contributory etiologies identified, including pre-existing alcoholic liver disease, hepatitis B and/or C infection, and concomitant usage of other potentially hepatotoxic drugs. Although clinically significant liver dysfunction is not typically recognized as a manifestation of opioid withdrawal, opioid withdrawal that is precipitated abruptly may lead to systemic sequelae including acute liver injury. 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. Depression and Suicidality: Alcohol- and opioid-dependent patients, 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: In controlled clinical trials of VIVITROL administered to adults with alcohol dependence, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in patients treated with VIVITROL than in patients treated with placebo (1% vs 0). In some cases, the suicidal thoughts or behavior occurred after study discontinuation, but were in the context of an episode of depression that began while the patient was on study drug. Two completed suicides occurred, both involving patients treated with VIVITROL. Depression-related events associated with premature discontinuation of study drug were also more common in patients treated with VIVITROL (~1%) than in placebo-treated patients (0). In the 24-week, placebo-controlled pivotal trial in 624 alcohol-dependent patients, 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: In an open-label, long-term safety study conducted in the US, adverse events of a suicidal nature (depressed mood, suicidal ideation, suicide attempt) were reported by 5% of opioid-dependent patients treated.
with VIVITROL 380 mg (n=101) and 10% of opioid-dependent patients treated with placebo. In 24-week, placebo-controlled pivotal trial that was conducted in Russia in 265 opioid-dependent patients, adverse events involving depressed mood or suicidal thinking were not reported by any patient in either treatment group (VIVITROL 380 mg or placebo). 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. If opioid therapy is required as part of anesthesia care setting by persons not specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the 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: In clinical trials with VIVITROL, there was one diagnosed case and one suspected case of eosinophilic pneumonia. Both cases required hospitalization, and resolved after treatment with antibiotics and corticosteroids. Similar cases have been reported in postmarketing use. Should a person receiving VIVITROL develop progressive dyspnea and hypoxemia, the diagnosis of eosinophilic pneumonia should be considered. 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 in 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. Intramuscular Injections: As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulopathy (eg, hemophilia and severe hepatic failure). Alcohol Withdrawal: Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms. Interference with Laboratory Tests: VIVITROL may be cross-reactive with certain immunoassay methods for the detection of drugs of abuse (specifically opioids) in urine. For further information, reference to the specific immunoassay instructions is recommended.

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 ≥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 therapy in opioid dependent patients (ie, those occurring in ≥ 2% and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In all controlled and uncontrolled trials during the premarketing development of VIVITROL, more than 1100 patients with alcohol and/or opioid dependence have been treated with VIVITROL. Approximately 700 patients have been treated for 6 months or more, and more than 400 for 1 year or longer. Adverse Events Leading to Discontinuation of Treatment: Alcohol Dependence: In controlled trials of 6 months or less in alcohol-dependent patients, 9% of alcohol-dependent patients treated with VIVITROL discontinued treatment due to an adverse event, as compared to 7% of the alcohol-dependent patients treated with placebo. Adverse events in the VIVITROL 380-mg group that led to more dropouts than in the placebo-treated group were injection site reactions (3%), nausea (2%), pregnancy (1%), headache (1%), and suicide-related events (0.3%). In the placebo group, 1% of patients withdrew due to injection site reactions, and 0% of patients withdrew due to the other adverse events. Opioid Dependence: In a controlled trial of 6 months, 2% of opioid-dependent patients treated with VIVITROL discontinued treatment due to an adverse event, as compared to 2% of the opioid-dependent patients treated with placebo.

DRUG INTERACTIONS: Patients taking VIVITROL may not benefit from opioid-containing medicines. Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics.

USE IN SPECIFIC POPULATIONS: Pregnancy: There are no adequate and well-controlled studies of either naltrexone or VIVITROL in pregnant women. VIVITROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy Category C: Reproduction and developmental studies have not been conducted for VIVITROL. Studies with naltrexone administered via the oral route have been conducted in pregnant rats and rabbits. Teratogenic Effects: Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥30 mg/kg/day (11 times the human exposure based on an AUC(0-28d) comparison) and to rabbits at oral doses ≥60 mg/kg/day (2 times the human exposure based on an AUC(0-28d) comparison). There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day (175- and 14-times the human exposure based on an AUC(0-28d) comparison, respectively). Labor and Delivery: The potential effect of VIVITROL on duration of labor and delivery in humans is unknown. Nursing Mothers: Transfer of naltrexone and 6-naltrexol into human milk has been reported with oral naltrexone. Because of the potential for tumorigenicity shown for naltrexone in animal studies, and because of the potential for serious adverse reactions in nursing infants from VIVITROL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Pediatric Use: There is limited experience with overdose of VIVITROL in pediatric use. Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms in infants from VIVITROL, the decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Pharmacokinetics of VIVITROL have not been evaluated in a pediatric population. Geriatric Use: In trials of alcohol-dependent subjects, 2.6% (n=26) of subjects were >65 years of age, and one patient was >75 years of age. Clinical studies of VIVITROL did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. No subjects over age 65 were included in studies of opioid-dependent subjects. The pharmacokinetics of VIVITROL have not been evaluated in the geriatric population. Pregnancy: Reproduction and developmental studies with naltrexone administered via the oral route have been conducted in pregnant rats and rabbits. The pharmacokinetics of VIVITROL have not been evaluated in subjects with mild renal insufficiency (creatinine clearance of 50-80 mL/min). Dose adjustment is not required in patients with mild renal impairment. VIVITROL pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency. Because naltrexone and its primary metabolite are excreted primarily in the urine, caution is recommended in administering VIVITROL to patients with moderate to severe renal impairment. Hepatic Impairment: The pharmacokinetics of VIVITROL are not altered in subjects with mild to moderate hepatic impairment (Groups A and B of the Child-Pugh classification). Dose adjustment is not required in subjects with mild or moderate hepatic impairment. VIVITROL pharmacokinetics were not evaluated in subjects with severe hepatic impairment.

OVERDOSAGE: There is limited experience with overdose of VIVITROL. Single doses up to 784 mg were administered to 5 healthy subjects. There were no serious or severe adverse events. The most common effects were injection site reactions, nausea, abdominal pain, somnolence, and dizziness. There were no significant increases in hepatic enzymes. In the event of an overdose, appropriate supportive treatment should be initiated.

This brief summary is based on VIVITROL Full Prescribing Information.

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