FOR THE TREATMENT OF 
ALKOHOL DEPENDENCE IN 
PATIENTS WHO ARE ABLE TO 
ABSTAIN FROM ALCOHOL IN AN 
OUTPATIENT SETTING PRIOR TO 
INITIATION OF TREATMENT, AND 
TOGETHER WITH COUNSELING

PLEASE SEE IMPORTANT SAFETY INFORMATION THROUGHOUT THIS BROCHURE. 
PLEASE ALSO SEE ACCOMPANYING PRESCRIBING INFORMATION AND 
MEDICATION GUIDE. REVIEW MEDICATION GUIDE WITH YOUR PATIENTS.
**HOW VIVITROL WORKS**

VIVITROL is a once-monthly antagonist therapy

Although the mechanism of action in alcohol dependence is not fully understood, this blockade is thought to prevent the increased dopamine release responsible for the pleasurable reinforcing effects of alcohol.  

**WHAT IS VIVITROL?**

VIVITROL is:
- Monthly extended-release injectable naltrexone (380 mg)
- HCP-administered
- Opioid antagonist
- Non-addictive
- Non-narcotic
- Not associated with diversion
- Requires detox
- Part of a comprehensive management program that includes psychosocial support

VIVITROL contains an opioid antagonist called naltrexone. The naltrexone is formulated in microspheres that break down slowly over the course of the month so that the antagonist can continue to block opioid receptors for four weeks.

Patients should not be actively drinking at the time of initial VIVITROL administration. It is recommended that patients stop taking opioids or opioid-containing medications for a minimum of 7-10 days before starting VIVITROL to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization.

**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

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.).

**IMPORTANT SAFETY INFORMATION**

**MEAN NALTREXONE CONCENTRATION**

Beginning approximately 14 days after dosing, concentrations slowly decline, with measurable levels for greater than 1 month.
VIVITROL IN ALCOHOL DEPENDENCE: PRIMARY STUDY ENDPOINT

Overall treatment population
In the overall treatment population, patients treated with VIVITROL 380 mg (n=205) demonstrated a 25% greater reduction in days of heavy drinking than those treated with placebo (n=209; HR=0.75 [0.60-0.94]; P=0.02).10

Patients treated with VIVITROL 380 mg and psychosocial support had 25% FEWER HEAVY DRINKING DAYS (P=0.02) than patients treated with placebo and psychosocial support.

Study Design: VIVITROL in alcohol dependence was studied in a 6-month, multicenter, double-blind trial with monthly injections. Participants were screened and randomized. Participants received an intramuscular injection every 4 weeks—a total of 6 injections over 24 weeks. 208 patients received VIVITROL 380 mg and 209 received placebo. All participants received psychosocial support, which consisted of 12 counseling sessions. Inclusion criteria: Adults (age 18 or older) who met the DSM-IV criteria for active alcohol dependence and had a minimum of 2 episodes of heavy drinking* per week in the 30 days before screening.

Exclusion Criteria: Evidence of liver failure, aspartate aminotransferase or alanine aminotransferase >3 times the upper limit of normal; any clinically medical condition deemed significant by study investigator; major depression with suicidal ideation, psychosis, or bipolar disorder; dependence on benzodiazepines, opiates, or cocaine within the past year; more than 7 days of inpatient treatment for substance abuse in the month prior to screening; use of opiates oral naltrexone or disulfiram in the 2 weeks before screening.

In the prespecified subset (n=53, or 8% of the total study population) the median patient who abstained for 7 days prior to randomization had significantly fewer heavy drinking days in the average month vs. those treated with placebo during the 6-month study.

The same treatment effects were not evident among the subset of patients (n=571, 92% of the total study population) who were actively drinking at the time of treatment initiation.

- WITHIN SUBSET, 92% FEWER DAYS OF HEAVY DRINKING WITH VIVITROL

**IMPORTANT SAFETY INFORMATION**

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.

**Inclusion criteria:**
- Adults (age 18 or older) who met the DSM-IV criteria for active alcohol dependence and had a minimum of 2 episodes of heavy drinking* per week in the 30 days before screening.

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*Heavy drinking was defined as ≥5 standard drinks per day for men and ≥4 standard drinks per day for women.
**ADVERSE REACTIONS**

ADVERSE REACTIONS OCCURRED IN ≥5% OF PATIENTS WITH ALCOHOL DEPENDENCE TREATED WITH VIVITROL AND OCCURRED MORE FREQUENTLY IN THE VIVITROL GROUP THAN IN THE PLACEBO GROUP

<table>
<thead>
<tr>
<th>Adverse Reaction/Preferred Term</th>
<th>VIVITROL 380 mg With Psychosocial Support (n=205)</th>
<th>Placebo With Psychosocial Support (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ISR</td>
<td>69%</td>
<td>50%</td>
</tr>
<tr>
<td>Injection site tenderness</td>
<td>45%</td>
<td>39%</td>
</tr>
<tr>
<td>Injection site induration</td>
<td>35%</td>
<td>8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>33%</td>
<td>11%</td>
</tr>
<tr>
<td>Headache</td>
<td>25%</td>
<td>18%</td>
</tr>
<tr>
<td>Asthenic conditions</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>Other ISR (primarily nodules, swelling)</td>
<td>15%</td>
<td>4%</td>
</tr>
<tr>
<td>Insomnia, sleep disorder</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Vomiting NOS</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Anorexia, appetite decreased NOS, appetite disorder NOS</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness, syncope</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Arthralgia, arthritis, joint stiffness</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Depression</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Injection site ecchymosis</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Back pain, back stiffness</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Rash</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Somnolence, sedation</td>
<td>4%</td>
<td>1%</td>
</tr>
</tbody>
</table>

ISR=Injection site reaction; NOS=not otherwise specified.

Please see complete list of adverse events in the VIVITROL Prescribing Information.

**IMPORTANT SAFETY INFORMATION**

**Injection Site Reactions (cont’d):**
- 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.

**VIVITROL WAS ASSOCIATED WITH A 29% REDUCTION IN OVERALL COSTS IN ALCOHOL-DEPENDENT PATIENTS**

TOTAL HEALTHCARE COSTS OVER A 6-MONTH POST-INDEX PERIOD (INPATIENT, OUTPATIENT, AND PHARMACY COSTS)

<table>
<thead>
<tr>
<th>Cost per Patient</th>
<th>Pre-index</th>
<th>Post-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>$9467</td>
<td>$6757</td>
<td></td>
</tr>
</tbody>
</table>

VIVITROL was associated with a 29% reduction in overall costs in alcohol-dependent patients. (n=661)

**Study Design:** In this 2005-2009 retrospective database analysis, eligible adults were identified from a large US health plan and the IMS PharmMetrics Integrated Database. Included in this data are the medical and pharmacy claims from all available healthcare sites. During the pre- or post-index period, patients were required to have at least 1 claim for alcohol dependence (DSM-IV, code 303.xx), have an alcohol use disorder diagnosis pre-index, and have at least 6 months of continuous enrollment pre- and post-index. The index date is defined as the first medical claim for a nonpharmacologic treatment, such as a detoxification facility claim, a substance abuse treatment facility claim, or a substance abuse counseling claim. The index date for individuals in the “any medication” group is set as the earliest claim for alcohol medication. Patients in the “nonpharmacologic substance” group had no prescription fills for alcohol medication, while patients in the “any medication” group had at least 1 fill for any of the 4 alcoholism medications. VIVITROL was identified on the basis of outpatient drug claims using the National Drug Codes and on medical claims with the Healthcare Common Procedure Coding System code. With the exception of the XR-NTX group, (which was occasionally required to demonstrate prior oral medication failure), patients experiencing liver failure during the pre-index period who had claims for pharmacological treatment in the month prior to the index date were excluded.

**Limitations:** Findings in the study design represent associations, but not necessarily causality. The lack of quantitative measures on baseline alcohol use, precise contribution of medication, or the type of medication cannot be determined. It is also impossible to compare reduction in alcohol quantity or frequency across conditions. Additionally, the time frame for outcomes was limited to 6 months and only included subjects who were commercially insured with 1 year of continuous enrollment. Lastly, the XR-NTX sample was smaller than others and no information was available for the recommended duration of treatment.

This study was funded by Alkermes, Inc.

**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.**
IMPORTANT SAFETY INFORMATION

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 intramuscular 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.

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IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

- 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), arthralgia, arthritis, or joint stiffness, 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 ≥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.

For more information about alcohol dependence, contact your ALKERMES representative.