

Laboratory Tests

Eosinophil Count

In clinical trials, subjects on VIVITROL had increases in eosinophil counts relative to subjects on placebo. With continued use of VIVITROL, eosinophil counts returned to normal over a period of several months.

Platelet Count

VIVITROL 380 mg was associated with a decrease in platelet count. In clinical trials, alcohol-dependent patients treated with VIVITROL experienced a mean maximal decrease in platelet count of $17.8 \times 10^3/\mu\text{L}$, compared to $2.6 \times 10^3/\mu\text{L}$ in placebo patients.

After 24 weeks of treatment, opioid-dependent patients treated with VIVITROL experienced a mean maximal decrease in platelet count of $62.8 \times 10^3/\mu\text{L}$, compared to $39.9 \times 10^3/\mu\text{L}$ in placebo patients. In randomized controlled trials, VIVITROL was not associated with an increase in bleeding-related adverse events.

Hepatic Enzyme Elevations

In short-term, controlled trials, in alcohol-dependent patients, the incidence of AST elevations associated with VIVITROL treatment was similar to that observed with oral naltrexone treatment (1.5% each) and slightly higher than observed with placebo treatment (0.9%).

In the 6-month controlled trial conducted in opioid-dependent subjects, 89% had a baseline diagnosis of hepatitis C infection, and 41% had a baseline diagnosis of HIV infection. There were frequently observed elevated liver enzyme levels (ALT, AST, and GGT); these were more commonly reported as adverse events in the VIVITROL 380 mg group than in the placebo group. Patients could not enroll in this trial if they had a baseline ALT or AST value that was more than three times the upper limit of normal. More patients treated with VIVITROL in this study experienced treatment-emergent elevations in transaminases to more than three times the upper limit of normal than patients treated with placebo. Shifts to more than three times the upper limit of normal occurred in 20% of patients treated with VIVITROL as compared with 13% of placebo patients. Shifts in values of AST to more than three times the upper limit were also more common in the VIVITROL (14%) arm compared with the placebo (11%) arm. Opioid-dependent patients treated with VIVITROL experienced a mean maximal increase from baseline ALT levels of 61 IU/L compared with 48 IU/L in placebo patients. Similarly for AST, opioid-dependent patients treated with VIVITROL experienced a mean maximal increase from baseline AST levels of 40 IU/L compared with 31 IU/L in placebo patients.

Creatinine Phosphokinase

In short-term controlled trials in alcohol-dependent patients, more patients treated with VIVITROL 380 mg (11%) and oral naltrexone (17%) shifted from normal creatinine phosphokinase (CPK) levels before treatment to abnormal CPK levels at the end of the trials, compared to placebo patients (8%). In open-label trials, 16% of patients dosed for more than 6 months had increases in CPK. For both the oral naltrexone and VIVITROL 380 mg groups, CPK abnormalities were most frequently in the range of 1–2 × ULN. However, there were reports of CPK abnormalities as high as 4x ULN for the oral naltrexone group, and 35 × ULN for the VIVITROL 380 mg group. Overall, there were no differences between the placebo and naltrexone (oral or injectable) groups with respect to the proportions of patients with a CPK

value at least three times the upper limit of normal. No factors other than naltrexone exposure were associated with the CPK elevations.

More opioid-dependent patients treated with VIVITROL 380 mg (39%) shifted from normal creatinine phosphokinase (CPK) levels before treatment to abnormal CPK levels during the study as compared to patients treated with placebo (32%). There were reports of CPK abnormalities as high as $41.8 \times \text{ULN}$ for the placebo group, and $22.1 \times \text{ULN}$ for the VIVITROL 380 mg group.

Other Events Observed During the VIVITROL Clinical Studies

The following is a list of treatment-emergent adverse reactions reported by alcohol- and/or opioid-dependent subjects treated with VIVITROL in all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events that were so general as to be uninformative, and those events reported only once that did not have a substantial probability of being acutely life-threatening.

Blood and Lymphatic System Disorders – lymphadenopathy (including cervical adenitis), white blood cell count increased

Cardiac Disorders – angina pectoris, angina unstable, atrial fibrillation, cardiac failure congestive, coronary artery atherosclerosis, myocardial infarction, palpitations

Eye Disorders – conjunctivitis, vision blurred

Gastrointestinal Disorders – abdominal discomfort, colitis, constipation, flatulence, gastroesophageal reflux disease, gastrointestinal hemorrhage, hemorrhoids, pancreatitis acute, paralytic ileus, perirectal abscess

General Disorders and Administration Site Conditions – chest pain, chest tightness, chills, face edema, irritability, lethargy, pyrexia, rigors

Hepatobiliary Disorders – cholecystitis acute, cholelithiasis

Immune System Disorders – seasonal allergy, hypersensitivity reaction (including angioneurotic edema and urticaria)

Infections and Infestations – bronchitis, gastroenteritis, laryngitis, pneumonia, sinusitis, tooth abscess, upper respiratory tract infection, urinary tract infection, advanced HIV disease in HIV-infected patients

Investigations – weight decreased, weight increased

Metabolism and Nutrition Disorders – appetite increased, dehydration, heat exhaustion, hypercholesterolemia

Musculoskeletal and Connective Tissue Disorders – joint stiffness, muscle spasms, myalgia, pain in limb

Nervous System Disorders – cerebral arterial aneurysm, convulsions, disturbance in attention, dysgeusia, mental impairment, migraine, ischemic stroke, paresthesia

Pregnancy, Puerperium, and Perinatal Conditions – abortion missed

Psychiatric Disorders – abnormal dreams, agitation, alcohol withdrawal syndrome, euphoric mood, delirium, libido decreased

Respiratory, Thoracic, and Mediastinal Disorders – chronic obstructive pulmonary disease, dyspnea, pharyngolaryngeal pain, sinus congestion

Skin and Subcutaneous Tissue Disorders – night sweats, pruritus, sweating increased

Vascular Disorders – deep venous thrombosis, hot flushes, pulmonary embolism

6.2 Postmarketing Experience

Adverse Events Following Patient Self-Administration

Adverse events including injection site reactions and precipitated opioid withdrawal resulting in serious outcomes, including hospitalization, have been reported following patient self-administration of VIVITROL. VIVITROL must be prepared and administered by a healthcare provider.

Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions including anaphylaxis have been reported during postmarketing surveillance.

Reports From Other Intramuscular Drug Products Containing Polylactide-co-glycolide (PLG) Microspheres

Retinal Artery Occlusion

Retinal artery occlusion after injection with another drug product containing polylactide-co-glycolide (PLG) microspheres has been reported very rarely during postmarketing surveillance. This event has been reported in the presence of abnormal arteriovenous anastomosis. No cases of retinal artery occlusion have been reported during VIVITROL clinical trials or postmarketing surveillance. VIVITROL should be administered by intramuscular (IM) injection into the gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel [*see Dosage and Administration (2)*].

7 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data from published case series with VIVITROL use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are clinical considerations (*see Clinical Considerations*). Reproduction and developmental animal studies have not been conducted for VIVITROL. Daily oral administration of naltrexone to female rats and rabbits increased the incidence of early fetal

loss at exposures ≥ 11 times and ≥ 2 times the human exposure, respectively. Daily oral administration of naltrexone to pregnant rats and rabbits during the period of organogenesis did not induce malformation at exposures up to 175 times and 14 times the human exposure, respectively (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death. In addition, untreated opioid addiction often results in continued or relapsing illicit opioid use.

Published studies have demonstrated that alcohol is associated with fetal harm including growth restriction, facial abnormalities, central nervous system abnormalities, behavioral disorders, and impaired intellectual development.

Data

Animal Data

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.

Daily oral administration of 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).

Daily oral administration of naltrexone to rats and rabbits during the period of organogenesis did not induce malformations at doses up to 200 mg/kg/day (175- and 14-times the human exposure based on an $AUC_{(0-28d)}$ comparison, respectively).

8.2 Lactation

Risk Summary

Naltrexone and its major metabolite, 6 β -naltrexol, are present in human milk. There are no data on the effects on the breastfed infant or the effects on milk production. The developmental health benefits of breastfeeding should be considered along with the mother's clinical need for naltrexone and any potential adverse effects on the breastfed infant from naltrexone or the mother's underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy of VIVITROL have not been established in the pediatric population. The pharmacokinetics of VIVITROL have not been evaluated in a pediatric population.

8.5 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.

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

8.6 Renal Impairment

Pharmacokinetics of VIVITROL are not altered 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 [see *Clinical Pharmacology* (12.3)].

8.7 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 [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

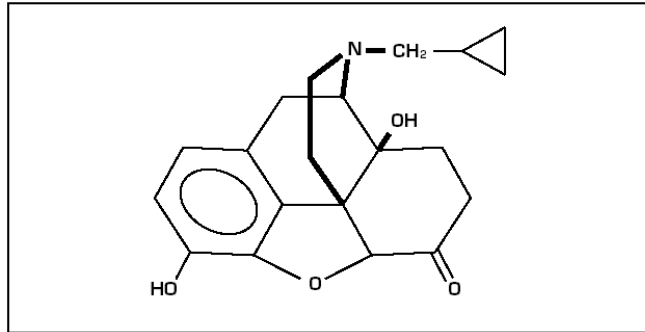
There is limited experience with overdose of VIVITROL. Single doses up to 784 mg were administered to 5 healthy subjects. There were no serious or severe adverse events. The most common effects were injection site reactions, nausea, abdominal pain, somnolence, and dizziness. There were no significant increases in hepatic enzymes.

In the event of an overdose, appropriate supportive treatment should be initiated.

11 DESCRIPTION

VIVITROL[®] (naltrexone for extended-release injectable suspension) is supplied as a microsphere formulation of naltrexone for suspension, to be administered by intramuscular injection. Naltrexone is an opioid antagonist with little, if any, opioid agonist activity.

Naltrexone is designated chemically as morphinan-6-one, 17 (cyclopropylmethyl) 4,5-epoxy-3,14-dihydroxy-(5 α) (CAS Registry # 16590-41-3). The molecular formula is C₂₀H₂₃NO₄ and its molecular weight is 341.41 in the anhydrous form (ie, < 1% maximum water content). The structural formula is:



Naltrexone base anhydrous is an off-white to a light tan powder with a melting point of 168-170°C (334-338°F). It is insoluble in water and is soluble in ethanol.

VIVITROL is provided as a carton containing a vial each of VIVITROL microspheres and diluent, one 5-mL syringe, one 1-inch 20-gauge preparation needle, two 1 1/2-inch 20-gauge and two 2-inch 20-gauge administration needles with needle protection device.

VIVITROL microspheres consist of a sterile, off-white to light tan powder that is available in a dosage strength of 380 mg of naltrexone per vial. Naltrexone is incorporated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres.

The diluent is a clear, colorless solution. The composition of the diluent includes carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection. The microspheres must be suspended in the diluent prior to injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has little or no opioid agonist activity.

12.2 Pharmacodynamics

Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

The administration of VIVITROL is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, VIVITROL will precipitate withdrawal symptomatology.

Occupation of opioid receptors by naltrexone may block the effects of endogenous opioid peptides. It markedly attenuates or completely blocks, reversibly, the subjective effects of exogenous opioids. The neurobiological mechanisms responsible for the reduction in alcohol consumption observed in alcohol-dependent patients treated with naltrexone are not entirely understood. However, involvement of the endogenous opioid system is suggested by preclinical data.

Naltrexone blocks the effects of opioids by competitive binding at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of opioids may result in non-opioid receptor-mediated symptoms such as histamine release.

VIVITROL is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opioid use or ethanol ingestion.

12.3 Pharmacokinetics

Absorption

VIVITROL is an extended-release, microsphere formulation of naltrexone designed to be administered by intramuscular (IM) gluteal injection every 4 weeks or once a month. After IM injection, the naltrexone plasma concentration time profile is characterized by a transient initial peak, which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2-3 days later. Beginning approximately 14 days after dosing, concentrations slowly decline, with measurable levels for greater than 1 month.

Maximum plasma concentration (C_{max}) and area under the curve (AUC) for naltrexone and 6β -naltrexol (the major metabolite) following VIVITROL administration are dose proportional. Compared to daily oral dosing with naltrexone 50 mg over 28 days, total naltrexone exposure is 3 to 4-fold higher following administration of a single dose of VIVITROL 380 mg. Steady state is reached at the end of the dosing interval following the first injection. There is minimal accumulation (<15%) of naltrexone or 6β -naltrexol upon repeat administration of VIVITROL.

Distribution

In vitro data demonstrate that naltrexone plasma protein binding is low (21%).

Elimination

The elimination half life of naltrexone following VIVITROL administration is 5-10 days and is dependent on the erosion of the polymer. The elimination half life of 6β -naltrexol following VIVITROL administration is 5-10 days.

Metabolism

Naltrexone is extensively metabolized in humans. Production of the primary metabolite, 6β -naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes. The cytochrome P450 system is not involved in naltrexone metabolism. Two other minor metabolites are 2-hydroxy-3-methoxy- 6β -naltrexol and 2-hydroxy-3-methoxy-naltrexone. Naltrexone and its metabolites are also conjugated to form glucuronide products.

Significantly less 6β -naltrexol is generated following IM administration of VIVITROL compared to administration of oral naltrexone due to a reduction in first-pass hepatic metabolism.

Excretion

Elimination of naltrexone and its metabolites occurs primarily via urine, with minimal excretion of unchanged naltrexone.

Specific Populations

Pediatric: Pharmacokinetics of VIVITROL have not been evaluated in a pediatric population.

Geriatric: Pharmacokinetics of VIVITROL have not been evaluated in the geriatric population [see *Use in Specific Populations (8.5)*].

Race: Effect of race on the pharmacokinetics of VIVITROL has not been studied.

Sex: In a study in healthy subjects (n=18 females and 18 males), sex did not influence the pharmacokinetics of VIVITROL.

Renal Insufficiency: A population pharmacokinetic analysis indicated mild renal insufficiency (creatinine clearance of 50-80 mL/min) had little or no influence on VIVITROL pharmacokinetics and that no dosage adjustment is necessary. VIVITROL pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency [see *Use in Specific Populations (8.6)*].

Hepatic Insufficiency: The pharmacokinetics of VIVITROL are not altered in subjects with mild to moderate hepatic impairment (Groups A and B of the Child-Pugh classification). VIVITROL pharmacokinetics were not evaluated in subjects with severe hepatic impairment [see *Use in Specific Populations (8.7)*].

Drug Interactions

In Vitro Studies: Because naltrexone is not a substrate for CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes are unlikely to change the clearance of VIVITROL. An in vitro CYP inhibition study demonstrated that naltrexone is not an inhibitor of major CYP enzymes (CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4). An in vitro CYP induction study demonstrated that naltrexone is not an inducer of CYP3A4 and CYP1A2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies have not been conducted with VIVITROL.

Carcinogenicity studies of oral naltrexone hydrochloride (administered via the diet) have been conducted in rats and mice.

In a two-year carcinogenicity study in rats, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The incidence of testicular mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day (3-times the human exposure based on an AUC_(0-28d) comparison) was 6%, compared with a maximum historical incidence of 4%. The incidence of vascular tumors in males and females given dietary doses of 100 mg/kg/day was 4% but only the incidence in females was increased compared with a maximum historical control incidence of 2% (3 and 32 times the human exposure based on an AUC_(0-28d) comparison in males and females, respectively). There was no evidence of carcinogenicity in a 2-year dietary study with naltrexone in male and female mice (12 and 3 times the human exposure based on an AUC_(0-28d) comparison, respectively). The clinical significance of these findings is not known.

Mutagenesis: Naltrexone was negative in the following in vitro genotoxicity studies: bacterial reverse mutation assay (Ames test), the heritable translocation assay, CHO cell sister chromatid exchange assay, and the mouse lymphoma gene mutation assay. Naltrexone was also negative in an in vivo mouse micronucleus assay. In contrast, naltrexone tested positive in the following assays: *Drosophila* recessive lethal frequency assay, non-specific DNA damage in repair tests with *E. coli* and WI-38 cells, and urinalysis for methylated histidine residues.

Impairment of Fertility: Daily oral administration of naltrexone caused a significant increase in pseudopregnancy and a decrease in pregnancy rates in rats at 100 mg/kg/day (75 times the human exposure based on an $AUC_{(0-28d)}$ comparison). There was no effect on male fertility at this dose level (6 times the human exposure based on an $AUC_{(0-28d)}$ comparison). The relevance of these observations to human fertility is not known.

14 CLINICAL STUDIES

Alcohol Dependence

The efficacy of VIVITROL in the treatment of alcohol dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of alcohol-dependent (DSM-IV criteria) outpatients. Subjects were treated with an injection every 4 weeks of VIVITROL 190 mg, VIVITROL 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Psychosocial support was provided to all subjects in addition to medication.

Subjects treated with VIVITROL 380 mg demonstrated a greater reduction in days of heavy drinking than those treated with placebo. Heavy drinking was defined as self-report of 5 or more standard drinks consumed on a given day for male patients and 4 or more drinks for female patients. Among the subset of patients ($n=53$, 8% of the total study population) who abstained completely from drinking during the week prior to the first dose of medication, compared with placebo-treated patients, those treated with VIVITROL 380 mg had greater reductions in the number of drinking days and the number of heavy drinking days. In this subset, patients treated with VIVITROL were also more likely than placebo-treated patients to maintain complete abstinence throughout treatment. 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.

Opioid Dependence

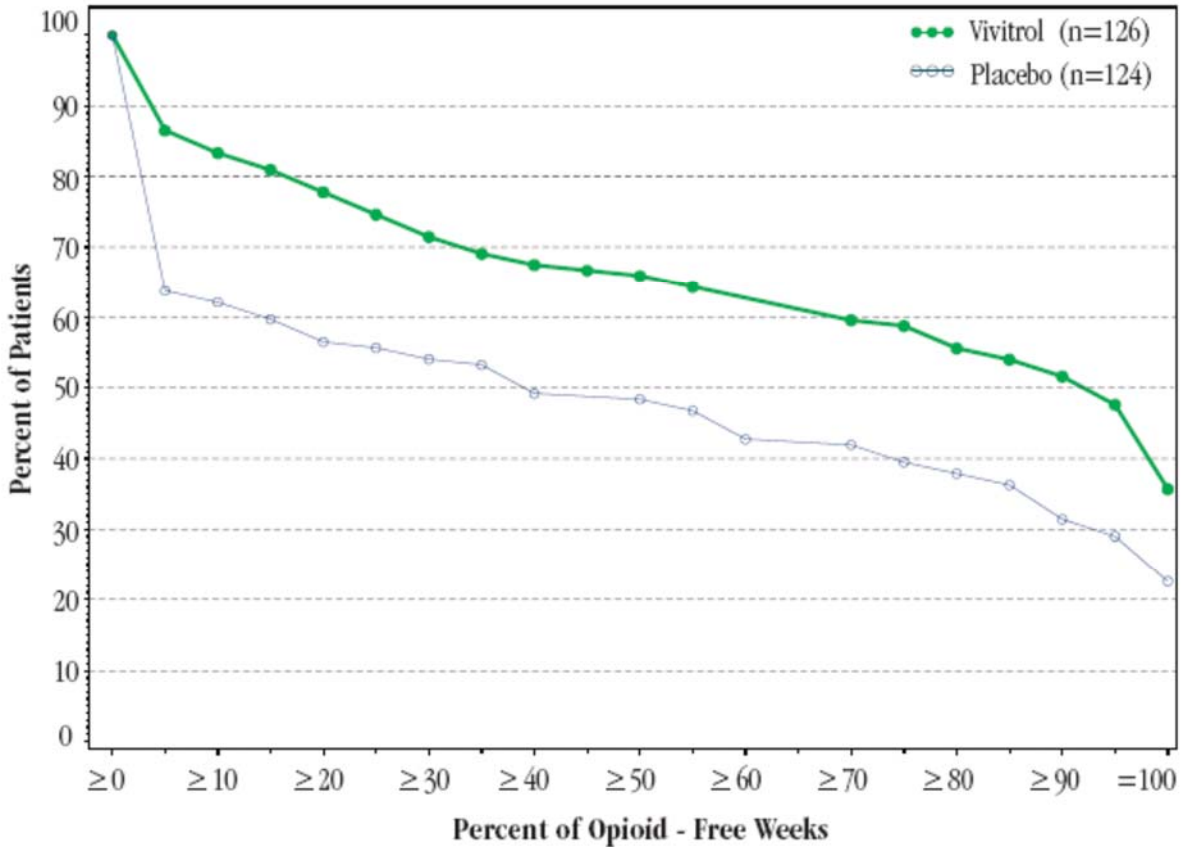
The efficacy of VIVITROL in the treatment of opioid dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of opioid-dependent (DSM-IV) outpatients, who were completing or had recently completed detoxification. Subjects were treated with an injection every 4 weeks of VIVITROL 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Standardized, manual-based psychosocial support was provided on a biweekly basis to all subjects in addition to medication.

Figure 1, below, displays the cumulative percentage of subjects with opioid-free weeks ranging from no visits (0%) to all visits (100%). An opioid-free week was one in which urine drug test results were negative for opioids and self-reported opioid use was also zero. An initial period of

engagement in treatment was permitted during which opiate use, if it occurred, was not considered in the analysis. Subjects discontinuing from the trial were assumed to have had opioid-use weeks for the weeks after dropout.

The cumulative percentage of subjects achieving each observed percentage of opioid-free weeks was 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.

Figure 1: Subjects Sustaining Varying Percentages of Opioid-Free Weeks



A greater percentage of subjects in the VIVITROL group remained in the study compared to the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

VIVITROL (naltrexone for extended-release injectable suspension) is supplied in single-use cartons. Each carton contains one 380 mg vial of VIVITROL microspheres, one vial containing 4 mL (to deliver 3.4 mL) of diluent for the suspension of VIVITROL, one 5-mL prepackaged syringe, one 1-inch 20-gauge needle, two 1 1/2-inch 20-gauge needles and two 2-inch 20-gauge needles with needle protection devices: NDC 65757-300-01.

VIVITROL must be prepared and administered by a healthcare provider.

16.1 Storage and Handling

The entire dose pack should be stored in the refrigerator (2 to 8°C, 36 to 46°F). Unrefrigerated, VIVITROL can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose the product to temperatures above 25°C (77°F). VIVITROL should not be frozen.

Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. A properly mixed suspension will be milky white, will not contain clumps, and will move freely down the wall of the vial [*see Dosage and Administration (2.5)*].

Keep out of Reach of Children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved patient labeling (Medication Guide).

Physicians should include the following issues in discussions with patients for whom they prescribe VIVITROL:

- Advise patients that if they previously used opioids, they may be more sensitive to lower doses of opioids and at risk of accidental overdose should they use opioids when their next dose is due, if they miss a dose, or after VIVITROL treatment is discontinued. 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.
- Advise patients that because VIVITROL can block the effects of opioids, patients will not perceive any effect if they attempt to self-administer heroin or any other opioid drug in small doses while on VIVITROL. Further, emphasize that administration of large doses of heroin or any other opioid to try to bypass the blockade and get high while on VIVITROL may lead to serious injury, coma, or death.
- Inform patients on VIVITROL that they may not experience the expected effects from opioid-containing analgesic, antidiarrheal, or antitussive medications.
- Instruct patients that VIVITROL must be prepared and administered by a healthcare provider.

- Advise patients that a reaction at the site of VIVITROL injection may occur. Reactions include pain, tenderness, induration, swelling, erythema, bruising, or pruritus. Serious injection site reactions including necrosis may occur. Some of these injection site reactions have required surgery. Patients should be advised to seek medical attention for worsening skin reactions.
- Advise patients that they should be off all opioids, including opioid-containing medicines, for a minimum of 7 – 10 days before starting VIVITROL in order to avoid precipitation of opioid withdrawal. Patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as two weeks. Ensure that patients understand that withdrawal precipitated by administration of an opioid antagonist may be severe enough to require hospitalization if they have not been opioid-free for an adequate period of time, and is different from the experience of spontaneous withdrawal that occurs with discontinuation of opioid in a dependent individual. Advise patients that they should not take VIVITROL if they have any symptoms of opioid withdrawal. Advise all patients, including those with alcohol dependence, that it is imperative to notify healthcare providers of any recent use of opioids or any history of opioid dependence before starting VIVITROL to avoid precipitation of opioid withdrawal.
- Advise patients that VIVITROL may cause liver injury. Patients should immediately notify their physician if they develop symptoms and/or signs of liver disease.
- Advise patients that they may experience depression while taking VIVITROL. It is important that patients inform family members and the people closest to the patient that they are taking VIVITROL and that they should call a doctor right away should they become depressed or experience symptoms of depression.
- Advise patients to carry documentation to alert medical personnel to the fact that they are taking VIVITROL (naltrexone for extended-release injectable suspension). This will help to ensure that patients obtain adequate medical treatment in an emergency.
- Advise patients that VIVITROL may cause an allergic pneumonia. Patients should immediately notify their physician if they develop signs and symptoms of pneumonia, including dyspnea, coughing, or wheezing.
- Advise patients that they should not take VIVITROL if they are allergic to VIVITROL or any of the microsphere or diluent components.
- Advise patients that they may experience nausea following the initial injection of VIVITROL. These episodes of nausea tend to be mild and subside within a few days post-injection. Patients are less likely to experience nausea in subsequent injections. Patients should be advised that they may also experience tiredness, headache, vomiting, decreased appetite, painful joints and muscle cramps.
- Advise patients that because VIVITROL is an intramuscular injection and not an implanted device, once VIVITROL is injected, it is not possible to remove it from the body.

- Advise patients that VIVITROL has been shown to treat alcohol and opioid dependence only when used as part of a treatment program that includes counseling and support.
- Advise patients that dizziness may occur with VIVITROL treatment, and they should avoid driving or operating heavy machinery until they have determined how VIVITROL affects them.
- Advise patients to notify their physician if they:
 - become pregnant or intend to become pregnant during treatment with VIVITROL.
 - are breast-feeding.
 - experience respiratory symptoms such as dyspnea, coughing, or wheezing when taking VIVITROL.
 - experience any allergic reactions when taking VIVITROL.
 - experience other unusual or significant side effects while on VIVITROL therapy.

US Patent Nos. 5,792,477; 5,916,598; 6,194,006; 6,264,987; 6,331,317; 6,379,703; 6,379,704; 6,395,304; 6,403,114; 6,495,166; 6,534,092; 6,537,586; 6,596,316; 6,713,090; 6,667,061; 6,495,164; 6,939,033; 5,650,173; 5,654,008; 6,540,393; 6,705,757; 6,861,016

17.1 Frequently Asked Questions About Administering VIVITROL:

1. Can I prepare the suspension prior to my patient's arrival?

No. You may remove the carton from the refrigerator prior to the patient's arrival, but once the diluent is added to the VIVITROL microspheres, the dose should be mixed and the suspension administered immediately. It is very important to use proper aseptic technique when preparing the suspension [see *Dosage and Administration (2.5)*].

2. How much time do I have between preparing and administering the dose?

It is recommended that the suspension be administered *immediately* once the product has been suspended and transferred into the syringe. If a few minutes' delay occurs after suspension but before transfer into the syringe [see *Dosage and Administration (2.5; Figure D)*], the vial can be inverted a few times to resuspend and then transferred into the syringe for immediate use [see *Dosage and Administration (2.5)*].

3. Can I use needles other than those provided in the carton?

No. The needles in the carton are specially designed for administration of VIVITROL. Do not make any substitutions for components of the carton [see *Dosage and Administration (2.5)*].

4. The suspension is milky white upon mixing with the diluent. Is this normal?

Yes. VIVITROL microspheres will form a milky suspension when mixed with the provided diluent [see *Dosage and Administration (2.5)*].

5. What if a needle clog occurs during administration of the product?

If a clog occurs during administration, the needle should be withdrawn from the patient, capped with the attached needle protection device, and replaced with the spare administration needle. Gently push on the plunger until a bead of the suspension appears at the tip of the needle. The remainder of the suspension should then be administered into an adjacent site in the same gluteal region [see *Dosage and Administration (2.5)*].

For additional information, visit www.vivitrol.com or call 1-800-848-4876

Manufactured and marketed by:

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MEDICATION GUIDE

VIVITROL® (viv-i-trol) (naltrexone for extended-release injectable suspension)

Read this Medication Guide before you start receiving VIVITROL injections and each time you receive an injection. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about VIVITROL?

VIVITROL can cause serious side effects, including:

1. Risk of opioid overdose.

You can accidentally overdose in two ways.

- VIVITROL blocks the effects of opioids, such as heroin or opioid pain medicines. **Do not** take large amounts of opioids, including opioid-containing medicines, such as heroin or prescription pain pills, to try to overcome the opioid-blocking effects of VIVITROL. This can lead to serious injury, coma, or death.
- After you receive a dose of VIVITROL, its blocking effect slowly decreases and completely goes away over time. If you have used opioid street drugs or opioid-containing medicines in the past, using opioids in amounts that you used before treatment with VIVITROL can lead to overdose and death. You may also be more sensitive to the effects of **lower** amounts of opioids:
 - after you have gone through detoxification
 - when your next VIVITROL dose is due
 - if you miss a dose of VIVITROL
 - after you stop VIVITROL treatment

It is important that you tell your family and the people closest to you of this increased sensitivity to opioids and the risk of overdose.

You or someone close to you should get emergency medical help right away if you:

- have trouble breathing
- become very drowsy with slowed breathing
- have slow, shallow breathing (little chest movement with breathing)
- feel faint, very dizzy, confused, or have unusual symptoms

2. Severe reactions at the site of the injection (injection site reactions).

Some people on VIVITROL have had severe injection site reactions, including tissue death (necrosis). Some of these injection site reactions have required surgery. VIVITROL must be injected by a healthcare provider. Call your healthcare provider right away if you notice any of the following at any of your injection sites:

- intense pain
- the area feels hard
- large area of swelling
- lumps
- blisters
- an open wound
- a dark scab

Tell your healthcare provider about any reaction at an injection site that concerns you, gets worse over time, or does not get better by two weeks after the injection.

3. Sudden opioid withdrawal.

Anyone who receives a VIVITROL injection must not use any type of opioid (must be opioid-free) including street drugs, prescription pain medicines, cough, cold, or diarrhea medicines that contain opioids, or opioid dependence treatments, buprenorphine or methadone, **for at least 7 to 14 days** before starting VIVITROL. Using opioids in the 7 to 14 days before you start receiving VIVITROL may cause you to suddenly have symptoms of opioid withdrawal when you get the VIVITROL injection. **Sudden opioid withdrawal can be severe, and you may need to go to the hospital.**

You must be opioid-free before receiving VIVITROL unless your healthcare provider decides that you don't need to go through detox first. Instead, your doctor may decide to give your VIVITROL injection in a medical facility that can treat you for sudden opioid withdrawal.

4. Liver damage or hepatitis.

Naltrexone, the active ingredient in VIVITROL, can cause liver damage or hepatitis.

Tell your healthcare provider if you have any of the following symptoms of liver problems during treatment with VIVITROL:

- stomach area pain lasting more than a few days
- dark urine
- yellowing of the whites of your eyes
- tiredness

Your healthcare provider may need to stop treating you with VIVITROL if you get signs or symptoms of a serious liver problem.

What is VIVITROL?

VIVITROL is a prescription injectable medicine used to:

- treat alcohol dependence. You should stop drinking before starting VIVITROL.
- prevent relapse to opioid dependence, **after** opioid detoxification.

This means that if you take opioids or opioid-containing medicines, you must stop taking them before you start receiving VIVITROL. **See “What is the most important information I should know about VIVITROL?”**

To be effective, treatment with VIVITROL must be used with other alcohol or drug recovery programs such as counseling. VIVITROL may not work for everyone.

It is not known if VIVITROL is safe and effective in children.

Who should not receive VIVITROL?

Do not receive VIVITROL if you:

- are using or have a physical dependence on opioid-containing medicines or opioid street drugs. **See “What is the most important information I should know about VIVITROL?”**

To see whether you have a physical dependence on opioid-containing medicines or opioid street drugs, your healthcare provider may give you a small injection of a medicine called naloxone. This is called a naloxone challenge test. **If you get symptoms of opioid withdrawal after the naloxone challenge test, do not start treatment with VIVITROL at that time.** Your healthcare provider may repeat the test after you have stopped using opioids to see whether it is safe to start VIVITROL.

- are having opioid withdrawal symptoms. Opioid withdrawal symptoms may happen when you have been taking opioid-containing medicines or opioid street drugs regularly and then stop.

Symptoms of opioid withdrawal may include: anxiety, sleeplessness, yawning, fever, sweating, teary eyes, runny nose, goose bumps, shakiness, hot or cold flushes, muscle aches, muscle twitches, restlessness, nausea and vomiting, diarrhea, or stomach cramps. **See “What is the most important information I should know about VIVITROL?”** Tell your healthcare provider if you have any of these symptoms before taking VIVITROL.

- are allergic to naltrexone or any of the ingredients in VIVITROL or the liquid used to mix VIVITROL (diluent). See the end of this Medication Guide for a complete list of ingredients in VIVITROL and the diluent.

What should I tell my healthcare provider before receiving VIVITROL?

Before you receive VIVITROL, tell your healthcare provider if you:

- have liver problems
- use or abuse street (illegal) drugs
- have hemophilia or other bleeding problems
- have kidney problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if VIVITROL will harm your unborn baby.
- are breastfeeding. It is not known if VIVITROL passes into your milk, and if it can harm your baby. Naltrexone, the active ingredient in VIVITROL, is the same active ingredient in tablets taken by mouth that contain naltrexone. Naltrexone from tablets passes into breast milk. Talk to your healthcare provider about whether you will breastfeed or take VIVITROL. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take any opioid-containing medicines for pain, cough or colds, or diarrhea. **See “What is the most important information I should know about VIVITROL?”**

If you are being treated for alcohol dependence but also use or are addicted to opioid-containing medicines or opioid street drugs, it is important that you tell your healthcare provider before starting VIVITROL to avoid having sudden opioid withdrawal symptoms when you start VIVITROL treatment.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive VIVITROL?

- VIVITROL is injected by a healthcare provider, about 1 time each month.
- VIVITROL must be injected by a healthcare provider. Do not attempt to inject yourself with VIVITROL. Serious reactions, some that may require hospitalization, might happen.
- VIVITROL is given as an injection into a muscle in your buttocks using a special needle that comes with VIVITROL.
- After VIVITROL is injected, it lasts for a month and it cannot be removed from the body.
- If you miss your appointment for your VIVITROL injection, schedule another appointment as soon as possible. **See “What is the most important information I should know about VIVITROL?”**
- Whenever you need medical treatment, be sure to tell the treating healthcare provider that you are receiving VIVITROL injections and mention when you got your last dose. This is important because VIVITROL can also block the effects of opioid-containing medicines that might be prescribed for you for pain, cough or colds, or diarrhea.
- Carry written information with you at all times to alert healthcare providers that you are taking VIVITROL, so that they can treat you properly in an emergency. Ask your healthcare provider how you can get a wallet card to carry with you.

What should I avoid while receiving VIVITROL?

Do not drive a car, operate machinery, or do other dangerous activities until you know how VIVITROL affects you. VIVITROL may make you feel dizzy and sleepy. **See “What are the possible side effects of VIVITROL?”**

What are the possible side effects of VIVITROL?

VIVITROL can cause serious side effects, including:

- See **“What is the most important information I should know about VIVITROL?”**
- **Depressed mood.** Sometimes this leads to suicide, or suicidal thoughts, and suicidal behavior. Tell your family members and people closest to you that you are taking VIVITROL.

You, a family member, or the people closest to you should call your healthcare provider right away if you become depressed or have any of the following symptoms of depression, especially if they are new, worse, or worry you:

- You feel sad or have crying spells.
 - You are no longer interested in seeing your friends or doing things you used to enjoy.
 - You are sleeping a lot more **or** a lot less than usual.
 - You feel hopeless or helpless.
 - You are more irritable, angry, or aggressive than usual.
 - You are more or less hungry than usual or notice a big change in your body weight.
 - You have trouble paying attention.
 - You feel tired or sleepy all the time.
 - You have thoughts about hurting yourself or ending your life.
- **Pneumonia.** Some people receiving VIVITROL treatment have had a certain type of pneumonia that is caused by an allergic reaction. If this happens to you, you may need to be treated in the hospital. Tell your healthcare provider right away if you have any of these symptoms during treatment with VIVITROL:
 - shortness of breath or wheezing
 - coughing that does not go away
 - **Serious allergic reactions.** Serious allergic reactions can happen during or soon after an injection of VIVITROL. Tell your healthcare provider or get medical help right away if you have any of these symptoms of a serious allergic reaction.
 - skin rash
 - swelling of your face, eyes, mouth, or tongue
 - trouble breathing or wheezing
 - chest pain
 - feeling dizzy or faint

Common side effects of VIVITROL may include:

- nausea. Nausea may happen after your first VIVITROL injection and usually improves within a few days. Nausea is less likely with future injections of VIVITROL.
- sleepiness
- headache
- dizziness
- vomiting

- decreased appetite
- painful joints
- muscle cramps
- cold symptoms
- trouble sleeping
- toothache

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the side effects of VIVITROL. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about VIVITROL

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about VIVITROL. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about VIVITROL that is written for health professionals.

For more information about VIVITROL call 1-800-848-4876, Option #1 or go to www.vivitrol.com.

What are the ingredients in VIVITROL?

Active ingredient: naltrexone

Inactive ingredients: polylactide-co-glycolide (PLG)

Diluent ingredients: carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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