

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIVITROL® safely and effectively. See full prescribing information for VIVITROL.

### VIVITROL® (naltrexone for extended-release injectable suspension) Intramuscular

Initial U.S. Approval: 1984

#### WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses and is contraindicated in acute hepatitis or liver failure. Use of VIVITROL should be discontinued in the event of symptoms or signs of acute hepatitis (5.1).

#### RECENT MAJOR CHANGES

Indications and Usage, Opioid Dependence (1.2)	10/2010
Dosage and Administration, Directions for Use (2.3)	08/2010

#### INDICATIONS AND USAGE

VIVITROL is an opioid antagonist. Opioid-dependent patients, including those being treated for alcohol dependence, must be opioid-free at the time of initial VIVITROL administration.

VIVITROL should be part of a comprehensive management program that includes psychosocial support.

- 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 (1.1).
- VIVITROL is indicated for the prevention of relapse to opioid dependence, following opioid detoxification (1.2).

#### DOSAGE AND ADMINISTRATION

The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month. The injection should be administered by a healthcare professional as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection, using the carton components provided (2 and 16.1).

**VIVITROL must not be administered intravenously or subcutaneously.** The entire dose pack should be stored in the refrigerator (2-8°C, 36-46°F) (2.3 and 16.1).

Do not expose the product to temperatures above 25°C (77°F). VIVITROL should not be frozen (2.3).

#### DOSAGE FORMS AND STRENGTHS

VIVITROL is an injectable suspension containing 380 mg of naltrexone in a microsphere formulation and 4 mL diluent (3).

#### CONTRAINDICATIONS

VIVITROL is contraindicated in:

- Patients with acute hepatitis or liver failure (5.1).
- Patients receiving opioid analgesics (5.5).
- Patients with current physiologic opioid dependence (5.5).
- Patients in acute opioid withdrawal (5.5).
- Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids (4).
- Patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent (4).

#### WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses and is contraindicated in acute

hepatitis or liver failure. Use of VIVITROL should be discontinued in the event of symptoms or signs of acute hepatitis (5.1).

- **Injection Site Reactions:** In some cases injection site reactions may be very severe. Some cases of injection site reactions required surgical intervention (5.2).
- **Eosinophilic pneumonia:** VIVITROL patients should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia (5.3).
- **Hypersensitivity:** Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis (5.4).
- **Unintended Precipitation of Opioid Withdrawal:** Opioid-dependent and opioid-using patients, including those being treated for alcohol dependence, must be opioid-free for a minimum of 7-10 days before starting VIVITROL treatment (5.5).
- **Opioid Overdose at the End of a Dosing Interval, After Missing a Dose and Following an Attempt to Overcome Opioid Blockade:** Use of lower doses of opioids after VIVITROL treatment is discontinued, at the end of a dosing interval, or after missing a dose could result in life-threatening opioid intoxication. Any attempt by a patient to overcome the blockade produced by VIVITROL by taking opioids is very dangerous and may lead to fatal overdose (5.6).
- **Depression and Suicidality:** VIVITROL patients should be monitored for the development of depression or suicidal thinking (5.7).
- **Intramuscular Injections:** VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder (5.8).
- **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 (5.9).

#### ADVERSE REACTIONS

The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (i.e., 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 (6).

The adverse events seen most frequently in association with VIVITROL therapy in opioid-dependent patients (i.e., 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 (6).

**To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-800-VIVITROL (1-800-848-4876) and/or email: [usmedinfo@alkermes.com](mailto:usmedinfo@alkermes.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### DRUG INTERACTIONS

Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics (7).

#### USE IN SPECIFIC POPULATIONS

- VIVITROL pharmacokinetics have not been evaluated in subjects with severe hepatic impairment (8.7).
- Caution is recommended in administering VIVITROL to patients with moderate to severe renal impairment (8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: October 2010

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## FULL PRESCRIBING INFORMATION

### **WARNING: HEPATOTOXICITY**

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. VIVITROL does not appear to be a hepatotoxin at the recommended doses.

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 [see *Warnings and Precautions (5.1)*]

## **1 INDICATIONS AND USAGE**

Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support. Opioid-dependent patients, including those being treated for alcohol dependence, must be opioid-free at the time of initial VIVITROL administration.

### **1.1 Alcohol Dependence**

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.

### **1.2 Opioid Dependence**

VIVITROL is indicated for the prevention of relapse to opioid dependence, following opioid detoxification.

## **2 DOSAGE AND ADMINISTRATION**

VIVITROL must be prepared and administered by a healthcare professional.

The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month. The injection should be administered by a healthcare professional as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection, using the carton components provided [see *How Supplied/Storage and Handling (16)*]. The needles provided in the carton are customized needles. VIVITROL must not be injected using any other needle. The needle lengths (either 1.5 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 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.

**VIVITROL must not be administered intravenously or subcutaneously.**

If a patient misses a dose, he/she should be instructed to receive the next dose as soon as possible.

Pretreatment with oral naltrexone is not required before using VIVITROL.

## **2.1 Reinitiation of Treatment in Patients Previously Discontinued**

There are no data to specifically address reinitiation of treatment. Patients reinitiating treatment with VIVITROL need to be opioid-free at the time of dose administration [*see Indications and Usage (1), Contraindications (4), and Warnings and Precautions (5.5)*].

## **2.2 Switching From Oral Naltrexone**

There are no systematically collected data that specifically address the switch from oral naltrexone to VIVITROL.

## **2.3 Directions for Use**

To ensure proper dosing, it is important that you follow the preparation and administration instructions outlined in this document.

VIVITROL must be suspended **only** in the diluent supplied in the carton and must be administered **only** with one of the administration needles supplied in the carton. The microspheres, diluent, preparation needle, and an administration needle with needle protection device are required for preparation and administration. Two thin-walled 1.5 inch needles with needle protection device are provided in the clinical drug cartons for intramuscular administration. In addition, longer 2 inch thin-walled needles with needle protection device have been provided as ancillary supplies. For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering health care professional may utilize the supplied 2 inch needle with needle protection device to ensure that the injectate reaches the intramuscular mass. Both 1.5 and 2 inch administration needles are provided to accommodate varying patient body habitus. A spare administration needle of each size is provided in case of clogging [*see How Supplied/Storage and Handling (16)*]. Do not substitute any other components for the components of the carton.

Prior to preparation, allow drug to reach room temperature (approximately 45 minutes).

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 Directions for Use, illustration below*].

Product to be prepared and administered by a healthcare professional.

Keep out of reach of children.

Prepare and administer the VIVITROL suspension using aseptic technique.

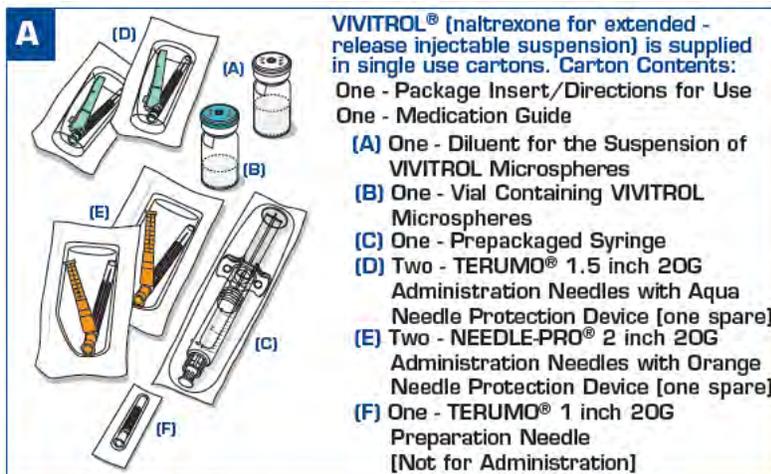
**WARNING:** To reduce the risk of a needlestick:

- Do not intentionally disengage the needle protection device.

- Discard bent or damaged needle into a sharps container and use the spare needle provided. Do not attempt to straighten the needle or engage needle protection device if the needle is bent or damaged.
- Do not mishandle the needle protection device in a way that could lead to protrusion of the needle.
- Do not use free hand to press sheath over needle.

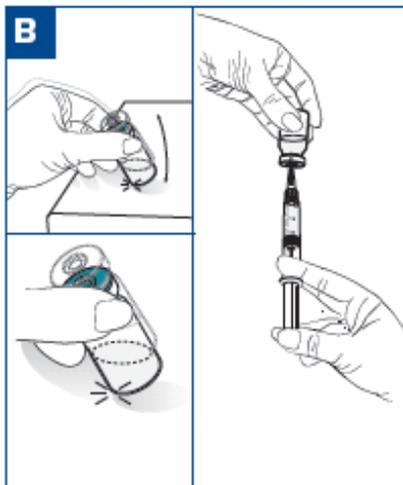
**THE CARTON SHOULD NOT BE EXPOSED TO TEMPERATURES EXCEEDING 25 °C (77 °F).**

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

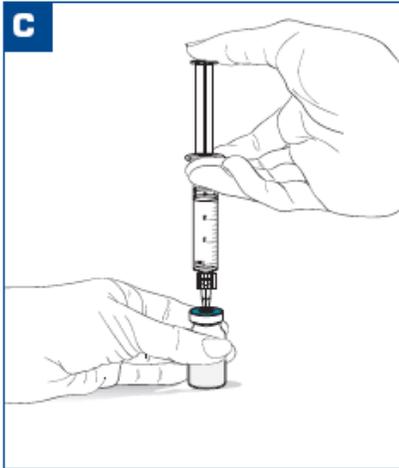


Parenteral products should be visually inspected for particulate matter and discoloration prior to administration.

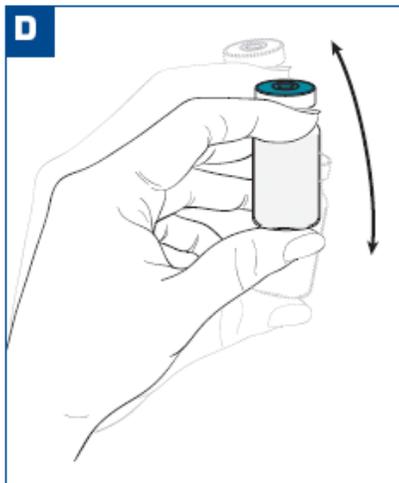
NEEDLE-PRO® and the color orange applied to the needle protection device are trademarks of the Smiths Medical family of companies.



1. Remove the carton from refrigeration. Prior to preparation, allow drug to reach room temperature (approximately 45 minutes).
2. To ease mixing, firmly tap the VIVITROL Microspheres vial on a hard surface, ensuring the powder moves freely. (see Figure B)
3. Remove flip-off caps from both vials. **DO NOT USE IF FLIP-OFF CAPS ARE BROKEN OR MISSING.**
4. Wipe the vial tops with an alcohol swab.
5. Place the 1 inch preparation needle on the syringe and withdraw 3.4 mL of the diluent from the diluent vial. Some diluent will remain in the diluent vial. (see Figure B)



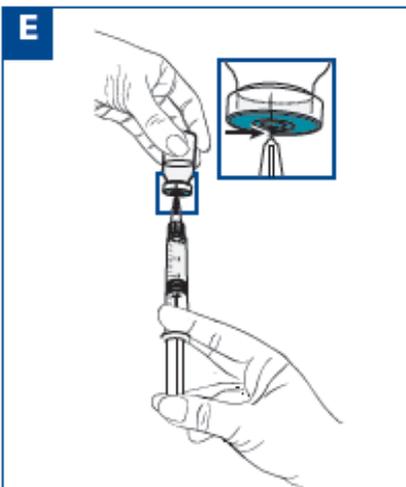
Inject the 3.4 mL of diluent into the VIVITROL Microsphere vial. (see Figure C)



Mix the powder and diluent by vigorously shaking the vial for approximately 1 minute. (see Figure D)

Ensure that the dose is thoroughly suspended prior to proceeding to Step E.

**A PROPERLY MIXED SUSPENSION WILL BE MILKY WHITE, WILL NOT CONTAIN CLUMPS, AND WILL MOVE FREELY DOWN THE WALLS OF THE VIAL.**



1. Immediately after suspension, withdraw 4.2 mL of the suspension into the syringe using the same preparation needle. (see Figure E)

2. Select the appropriate needle for an intramuscular injection based on patient's body habitus:

- a. 1.5 inch TERUMO<sup>®</sup> Needle
- b. 2 inch NEEDLE-PRO<sup>®</sup> Needle

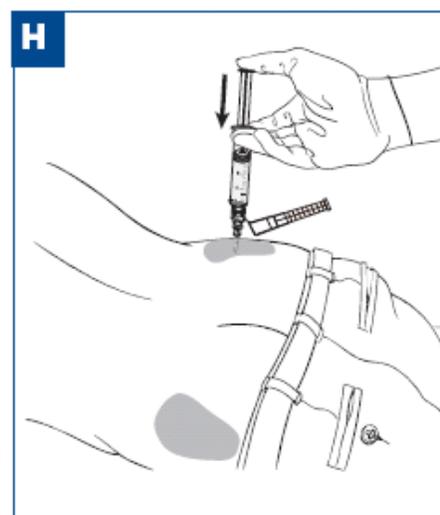


1. Remove the preparation needle and replace with appropriately selected administration needle for immediate use.
2. Peel the blister pouch of the selected administration needle open halfway. Grasp sheath using the plastic pouch. Attach the luer connection to the syringe with an easy clockwise twisting motion. (See Figure F)
3. Seat the needle firmly on the needle protection device with a push and clockwise twist.



1. Pull the sheath away from the needle – do not twist the sheath because it could result in loosening the needle.
2. Prior to injecting, tap the syringe to release any air bubbles, then push gently on the plunger until 4 mL of the suspension remains in the syringe. (see Figure G)

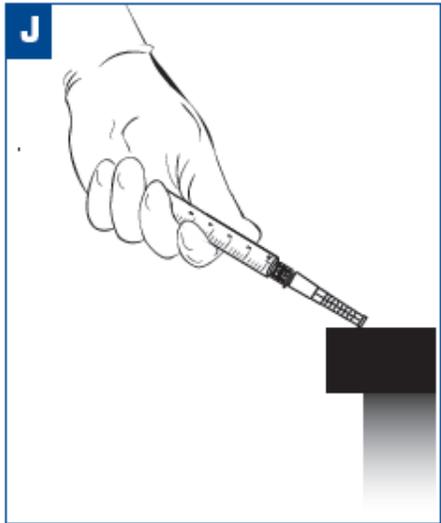
**THE SUSPENSION IS NOW READY FOR IMMEDIATE ADMINISTRATION.**



1. Administer the suspension by deep intramuscular (IM) injection into a gluteal muscle, alternating buttocks per monthly injection. **Remember to aspirate for blood before injection.** (see Figure H)
  2. If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the carton and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.
  3. Inject the suspension in a smooth and continuous motion.
- VIVITROL must NOT be given intravenously or subcutaneously.**



After the injection is administered, cover the needle by pressing the needle protection device against a flat surface using a one-handed motion away from self and others. (see Figure I)



Visually confirm needle is fully engaged into the needle protection device. (See Figure J)

**DISPOSE OF USED AND UNUSED ITEMS IN PROPER WASTE CONTAINERS.**

### 3 DOSAGE FORMS AND STRENGTHS

VIVITROL is an injectable suspension for single use. VIVITROL contains 380 mg of naltrexone in a microsphere formulation per vial (337 mg of naltrexone per gram of microspheres) and 4 mL diluent.

### 4. CONTRAINDICATIONS

VIVITROL is contraindicated in:

- Patients with acute hepatitis or liver failure [see *Warnings and Precautions (5.1)*]
- Patients receiving opioid analgesics [see *Warnings and Precautions (5.5)*].
- Patients with current physiologic opioid dependence [see *Warnings and Precautions (5.5)*].

- Patients in acute opioid withdrawal [*see Warnings and Precautions (5.5)*].
- Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids [*see Warnings and Precautions (5.5)*].
- Patients who have previously exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Hepatotoxicity**

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. VIVITROL does not appear to be a hepatotoxin at the recommended doses.

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.

### **5.2 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 1.5 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 [*see Patient Counseling Information (17)*]. 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.

### **5.3 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 [see *Adverse Reactions (6)*]. 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.

### **5.4 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.

### **5.5 Unintended Precipitation of Opioid Withdrawal**

To prevent occurrence of an acute abstinence syndrome (withdrawal) in patients dependent on opioids, or exacerbation of a pre-existing subclinical abstinence syndrome, opioid-dependent patients, including those being treated for alcohol dependence, must be opioid-free for a minimum of 7–10 days before starting VIVITROL treatment. Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a naloxone challenge test should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of VIVITROL. Patients treated for alcohol dependence with VIVITROL should be assessed for underlying opioid dependence and for any recent use of opioids prior to initiation of treatment with VIVITROL. 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 dependence on opioids.

### **5.6 Opioid Overdose at the End of a Dosing Interval, After Missing a Dose and Following an Attempt to Overcome Opioid Blockade**

After opioid detoxification, patients are likely to have reduced tolerance to opioids. Although VIVITROL blocks the effects of exogenous opioids for 28 days after administration, cases of opioid overdose with fatal outcomes have been reported in patients who used opioids at the end of a dosing interval or when missing a dose. Patients who have been treated with VIVITROL may respond to lower doses of opioids than previously used. This could result in potentially life-threatening opioid intoxication (.respiratory compromise or arrest, circulatory collapse, etc.). Patients should be aware that they may be more sensitive to lower doses of opioids after VIVITROL treatment is discontinued. Reduced tolerance is especially of concern at the end of a dosing interval, that is, near the end of the month after 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. [see *Patient Counseling Information (17)*].

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. 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 antagonism by taking opioids is very dangerous and may lead to fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life-endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opioid blockade [see Patient Counseling Information (17)].

## **5.7 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 professional.

### 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 which 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 oral naltrexone (n=20). In the 24-week, placebo-controlled pivotal trial that was conducted in Russia in 250 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).

## **5.8 Intramuscular Injections**

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

## **5.9 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 or analgesia, patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals 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.

## **5.10 Alcohol Withdrawal**

Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

## **5.11 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.

## **6 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 (i.e., those occurring in  $\geq 5\%$  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 (i.e., those occurring in  $\geq 2\%$  and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

## 6.1 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.

### Common Adverse Reactions

#### Alcohol Dependence

Table 1 lists all treatment-emergent clinical adverse reactions, regardless of causality, occurring in  $\geq 5\%$  of patients with alcohol dependence, for which the incidence was greater in the combined VIVITROL group than in the placebo group. A majority of patients treated with VIVITROL in clinical studies had adverse reactions with a maximum intensity of “mild” or “moderate”.

**Table 1: Treatment-emergent Adverse Reactions (Reactions in  $\geq 5\%$  of patients with alcohol dependence treated with VIVITROL and occurring more frequently in the combined VIVITROL group than in the placebo group)**

Body System	Adverse Reaction / Preferred Term	Placebo		Naltrexone for extended-release injectable suspension							
		N=214		400 mg N=25		380 mg N=205		190 mg N=210		All N=440	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal Disorders	Nausea	24	11	8	32	68	33	53	25	129	29
	Vomiting NOS	12	6	3	12	28	14	22	10	53	12
	Diarrhea)	21	10	3	12	27	13	27	13	57	13
	Abdominal painb)	17	8	4	16	23	11	23	11	50	11

Body System	Adverse Reaction / Preferred Term	Placebo		Naltrexone for extended-release injectable suspension							
		N=214		400 mg N=25		380 mg N=205		190 mg N=210		All N=440	
		N	%	N	%	N	%	N	%	N	%
	Dry Mouth	9	4	6	24	10	5	8	4	24	5
Infections & Infestations	Pharyngitis)	23	11	0	0	22	11	35	17	57	13
Psychiatric Disorders	Insomnia, sleep disorder	25	12	2	8	29	14	27	13	58	13
	Anxietyd)	17	8	2	8	24	12	16	8	42	10
	Depression	9	4	0	0	17	8	7	3	24	5
General Disorders & Administration Site Conditions	Any ISR	106	50	22	88	142	69	121	58	285	65
	Injection site tenderness	83	39	18	72	92	45	89	42	199	45
	Injection site induration	18	8	7	28	71	35	52	25	130	30
	Injection site pain	16	7	0	0	34	17	22	10	56	13
	Other ISR (primarily nodules, swelling)	8	4	8	32	30	15	16	8	54	12
	Injection site pruritus	0	0	0	0	21	10	13	6	34	8
	Injection site ecchymosis	11	5	0	0	14	7	9	4	23	5
	Asthenic conditionse)	26	12	3	12	47	23	40	19	90	20
Musculoskeletal & Connective Tissue Disorders	Arthralgia, arthritis, joint stiffness	11	5	1	4	24	12	12	6	37	9
	Back pain, back stiffness	10	5	1	4	12	6	14	7	27	6
	Muscle crampsf)	3	1	0	0	16	8	5	2	21	5
Skin & Subcutaneous Tissue Disorders	Rashg)	8	4	3	12	12	6	10	5	25	6
Nervous System Disorders	Headacheh)	39	18	9	36	51	25	34	16	94	21
	Dizziness, syncope	9	4	4	16	27	13	27	13	58	13
	Somnolence, sedation	2	1	3	12	8	4	9	4	20	5
Metabolism & Nutrition Disorders	Anorexia, appetite decreased NOS, appetite disorder NOS	6	3	5	20	30	14	13	6	48	11

- a) Includes the preferred terms: diarrhea NOS; frequent bowel movements; gastrointestinal upset; loose stools
- b) Includes the preferred terms: abdominal pain NOS; abdominal pain upper; stomach discomfort; abdominal pain lower
- c) Includes the preferred terms: nasopharyngitis; pharyngitis streptococcal; pharyngitis NOS
- d) Includes the preferred terms: anxiety NEC; anxiety aggravated; agitation; obsessive compulsive disorder; panic attack; nervousness; post-traumatic stress
- e) Includes the preferred terms: malaise; fatigue (these two comprise the majority of cases); lethargy; sluggishness
- f) Includes the preferred terms: muscle cramps; spasms; tightness; twitching; stiffness; rigidity
- g) Includes the preferred terms: rash NOS; rash papular; heat rash
- h) Includes the preferred terms: headache NOS; sinus headache; migraine; frequent headaches

## Opioid Dependence

In the open-label, long-term safety study conducted in the US, the commonly-reported adverse reactions among the opioid-dependent patients in the study were similar to those commonly observed events in the alcohol-dependent populations in VIVITROL clinical trials as displayed in [Table 1](#), above. For example, injection site reactions of all types, nausea and diarrhea occurred in more than 5% of patients on VIVITROL in the open-label study. In contrast, 48% percent, of the opioid-dependent patients had at least one adverse event in the “Infections and Infestations” Body System. Adverse Reactions/Preferred Terms of nasopharyngitis, upper respiratory tract infection, urinary tract infection, and sinusitis were most commonly reported.

In the placebo-controlled study in opioid-dependent patients conducted in Russia, the overall frequency of adverse events was lower than in the U.S. population described above. [Table 2](#) lists treatment-emergent clinical adverse events, regardless of causality, occurring in  $\geq 2\%$  of patients with opioid dependence, for which the incidence was greater in the VIVITROL group than in the placebo group. All adverse events were assessed as having a maximum intensity of “mild” or “moderate”.

**Table 2: Treatment-emergent Clinical Adverse Events (Events in  $\geq 2\%$  of patients with opioid dependence treated with VIVITROL and occurring more frequently in the VIVITROL group than in the placebo group)**

Body System	Adverse Event / Preferred Term	Placebo N=124		VIVITROL 380 mg N=126	
		n	%	n	%
Investigations	Alanine aminotransferase increased	7	6	16	13
	Aspartate aminotransferase increased	3	2	13	10
	Gamma-glutamyltransferase increased	4	3	9	7
Infections and Infestations	Nasopharyngitis	3	2	9	7
	Influenza	5	4	6	5
Psychiatric Disorders	Insomnia	1	1	8	6
Vascular Disorders	Hypertension	4	3	6	5
General Disorders and Administration Site Conditions	Injection site pain	1	1	6	5
Gastrointestinal Disorders	Toothache	2	2	5	4
Nervous System Disorders	Headache	3	2	4	3

### 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 x ULN. However, there were reports of CPK abnormalities as high as 4x ULN for the oral naltrexone group, and 35 x 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 x ULN for the placebo group, and 22.1 x 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 which were so general as to be uninformative, and those events reported only once which 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 Reports

### 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

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  $\geq 30$  mg/kg/day (11-times the human exposure based on an  $AUC_{(0-28d)}$  comparison) and to rabbits at oral doses  $\geq 60$  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<sub>(0-28d)</sub> comparison, respectively).

## **8.2 Labor and Delivery**

The potential effect of VIVITROL on duration of labor and delivery in humans is unknown.

## **8.3 Nursing Mothers**

Transfer of naltrexone and 6 $\beta$ -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.

## **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.

## **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

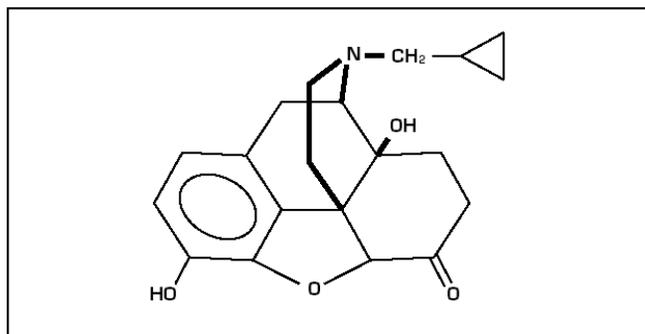
There is limited experience with overdose of VIVITROL. Single doses up to 784 mg were administered to 5 healthy subjects. There were no serious or severe adverse events. The most common effects were injection site reactions, nausea, abdominal pain, somnolence, and dizziness. There were no significant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

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

## 11 DESCRIPTION

VIVITROL<sup>®</sup> (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 $\alpha$ ) (CAS Registry # 16590-41-3). The molecular formula is C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub> and its molecular weight is 341.41 in the anhydrous form (i.e., < 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 1.5-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 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.

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

### 12.2 Pharmacodynamics

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 opiate 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 6 $\beta$ -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 6 $\beta$ -naltrexol upon repeat administration of VIVITROL.

#### Distribution

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

## **Metabolism**

Naltrexone is extensively metabolized in humans. Production of the primary metabolite, 6 $\beta$ -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-6 $\beta$ -naltrexol and 2-hydroxy-3-methoxy-naltrexone. Naltrexone and its metabolites are also conjugated to form glucuronide products.

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

## **Elimination**

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

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

## **Special 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.

*Gender:* In a study in healthy subjects (n=18 females and 18 males), gender 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 two-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: Naltrexone given via oral gavage 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.

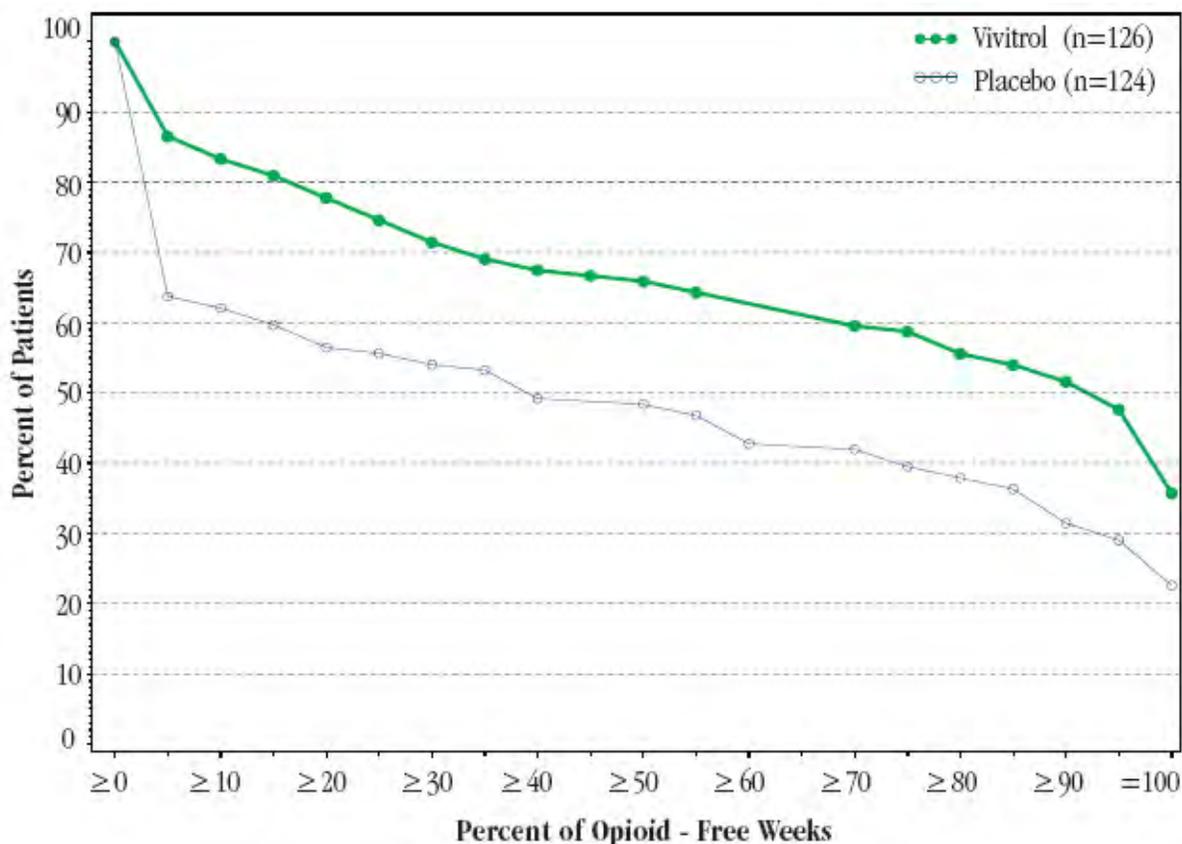
### Opioid Dependence

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) diluent for the suspension of VIVITROL, one 5-mL prepackaged syringe, one 1-inch 20-gauge needle, two 1.5-inch 20-gauge needles and two 2-inch 20-gauge needles with needle protection devices: NDC 65757-300-01.

### **16.1 Storage and Handling**

The entire dose pack should be stored in the refrigerator (2 - 8°C, 36 - 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* (2.3)].

**Keep out of Reach of Children.**

## **17 PATIENT COUNSELING INFORMATION**

See FDA-Approved Medication Guide.

### **17.1 Patient Information**

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

- 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. Patients should receive their injection from a healthcare professional qualified to administer the injection. Patients should be advised to seek medical attention for worsening skin reactions.
- Advise patients that they should be off all opioid-containing medicines (including methadone or buprenorphine) for 7– 10 days before starting VIVITROL in order to avoid precipitation of opioid withdrawal. Advise patients that they should not take VIVITROL if they have any symptoms of opioid withdrawal. Advise patients with alcohol dependence that it is imperative to notify health care professionals of any recent use of opioids or any history of opioid dependence before starting VIVITROL to avoid precipitation of opioid withdrawal.
- Advise patients that if they previously used opioids, they may be more sensitive to lower doses of opioids 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 administration of large doses of heroin or any other opioid while on VIVITROL may lead to serious injury, coma, or death. In addition, administration of previously-tolerated doses of opioids at the end of the dosing interval or after missing a dose may lead to overdose.
- Advise patients that because VIVITROL can block the effects of opiates and opiate-like drugs, patients will not perceive any effect if they attempt to self-administer heroin or any other opioid drug in small doses while on VIVITROL. Also, patients on VIVITROL may not experience the same effects from opioid-containing analgesic, antidiarrheal, or antitussive medications.
- Advise patients that VIVITROL may cause liver injury in people who develop liver disease from other causes. 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 that they should not take VIVITROL if they are allergic to VIVITROL or any of the microsphere or diluent components.
- 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 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 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.
- Patients should be advised of any other risks and information based on the clinical judgment of their physician.

**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**

## 17.2 Frequently Asked Questions:

### 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 (2.3)*].

### 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 (2.3; 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 (2.3)*].

### 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 (2.3)*].

### 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 (2.3)*].

### 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 (2.3)*].

For additional information, visit [www.vivitrol.com](http://www.vivitrol.com) or call 1-800-848-4876

Manufactured and marketed by:

Alkermes, Inc.

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## MEDICATION GUIDE

### VIVITROL® [vīv´-ī-trôl] (naltrexone for extended-release injectable suspension)

Read this Medication Guide before you start getting VIVITROL injections and each time you get an injection. There may be new information. This information does not take the place of talking to your doctor 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. Severe reactions at the site of injection
2. Liver damage or hepatitis
3. Risk of opioid overdose
4. Severe allergic pneumonia
5. Serious allergic reactions

**1. Severe reactions at the site of the injection.** Some people on VIVITROL treatment have had severe reactions at the site of the injection (injection site reactions), including tissue death (necrosis). Some of these injection site reactions have required surgery. Call your doctor right away if you have any of the following things happen 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 doctor 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.

**2. Liver damage or hepatitis.** Naltrexone, the active ingredient in Vivitrol, can cause liver damage (including liver failure) or hepatitis, if you take more than the recommended dose.

Tell your doctor 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 doctor may need to stop treating you with VIVITROL if you get signs or symptoms of a serious liver problem.

**3. Risk of Opioid Overdose.** If you have used opioid-containing medicines or opioid street drugs in the past, you may be more sensitive to lower doses of opioids:

- after VIVITROL treatment stops
- when your next VIVITROL dose is due
- if you miss a dose of VIVITROL

Using opioids in amounts that you used before treatment with VIVITROL can lead to overdose and death.

- You may not feel the usual effects if you use or abuse heroin and other illegal (street) opioids while on VIVITROL. Do not take large amounts of opioids, including opioid-containing medicines, such as prescription pain pills, or heroin, to overcome effects of VIVITROL. This can lead to overdose including serious injury, coma, or death.
- You may not feel the usual effects of opioid-containing medicines including medicines for pain, cough and diarrhea while on VIVITROL.
- 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**

**4. Severe allergic pneumonia.** Some people on VIVITROL treatment have had severe allergic pneumonia. Call your doctor if you have any of these symptoms:

- shortness of breath or wheezing
- coughing that does not go away

You may need to go to the hospital for treatment with antibiotic and steroid medicines.

**5. Serious allergic reactions.** Serious allergic reactions can happen during or soon after an injection of VIVITROL. Tell your doctor 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

6. Carry written information with you at all times to alert medical personnel that you are taking VIVITROL, so that they can treat you properly in an emergency.

### **What is VIVITROL?**

VIVITROL is a prescription injectable medicine used:

- to treat alcohol dependence
- to prevent relapse to opioid dependence, after opioid detoxification
- You should stop drinking before starting VIVITROL.
- If you take opioids or opioid-containing medicine, such as prescription pain medicines, you must stop these opioids or medicines before starting VIVITROL.
- To be effective, treatment with VIVITROL must be used with other alcoholism or drug recovery programs such as counseling.

VIVITROL may not work for everyone.

VIVITROL has not been studied in children under the age of 18 years.

### **Who should not take VIVITROL?**

Do not take VIVITROL if you:

- are using or have a physical dependence on opioid-containing medicines or opioid street drugs.
- You must not take opioid-containing medicines or opioid street drugs for 7 to 10 days before you start taking VIVITROL. 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 doctor 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 doctor may repeat the test after you have stopped using opioids to see whether it is safe to start VIVITROL.
- have opioid withdrawal symptoms.
  - Opioid withdrawal symptoms may happen when you have been taking opioid-containing medicines or opioid street drugs regularly

and then stop. These symptoms 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 doctor if you have any of these symptoms before taking VIVITROL.

- are allergic to VIVITROL or any of the ingredients in 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 doctor before starting VIVITROL?**

Tell your doctor about all of your medical conditions, including if you:

- have liver problems
- use opioid-containing medicines. **If you are being treated for alcoholism but also use or are addicted to opioid-containing medicines or opioid street drugs, it is important that you tell your doctor before starting VIVITROL to avoid having withdrawal symptoms when you start treatment.**
- use or abuse street (illegal) drugs
- have hemophilia or other bleeding problems
- have kidney problems
- 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 doctor about whether you will breast feed or take VIVITROL. You should not do both.

**Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. Especially tell your doctor 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?”)

### **How should I take VIVITROL?**

- VIVITROL is injected by a healthcare provider, about 1 time each month.
- VIVITROL is given as an injection into a muscle in your buttocks using a special needle that comes with VIVITROL.

- Once VIVITROL is injected, it lasts for a month and it cannot be removed from the body.
- If you miss your appointment for VIVITROL injection, schedule another appointment as soon as possible. See “What’s the most important information I should know about VIVITROL?”
- Whenever you need medical treatment, be sure to tell the treating doctor or nurse that you are receiving VIVITROL injections.

### **What should I avoid while taking VIVITROL?**

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

### **What are the possible side effects of VIVITROL?**

VIVITROL can cause serious side effects.

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

You or a family member should call your doctor 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.

Common side effects of VIVITROL include:

- nausea. Nausea usually improves within a few days after the first VIVITROL injection. Nausea is less likely with future injections of VIVITROL.

- tiredness
- headache
- dizziness
- vomiting
- decreased appetite
- painful joints
- muscle cramps

Common side effects in people taking VIVITROL for opioid dependence also include:

- cold symptoms
- trouble sleeping
- toothache

Tell your doctor about 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 doctor 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. VIVITROL was prescribed for your medical condition.

This leaflet summarizes the most important information about VIVITROL. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about VIVITROL that is written for health professionals.

For additional information about VIVITROL call 1-800-848-4876 or visit [www.vivitrol.com](http://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

Manufactured and marketed by:

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