Preventing Relapse to Opioid Dependence Following Opioid Detoxification

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

ALKERMES, INC. PROMOTIONAL PROGRAM

Vivitrol®
(naltrexone for extended-release injectable suspension) 380 mg/vial

Once-monthly dosing. Day by day control.

VIV 1040

Disease State

Vivitrol®
(naltrexone for extended-release injectable suspension) 380 mg/vial

Once-monthly dosing. Day by day control.

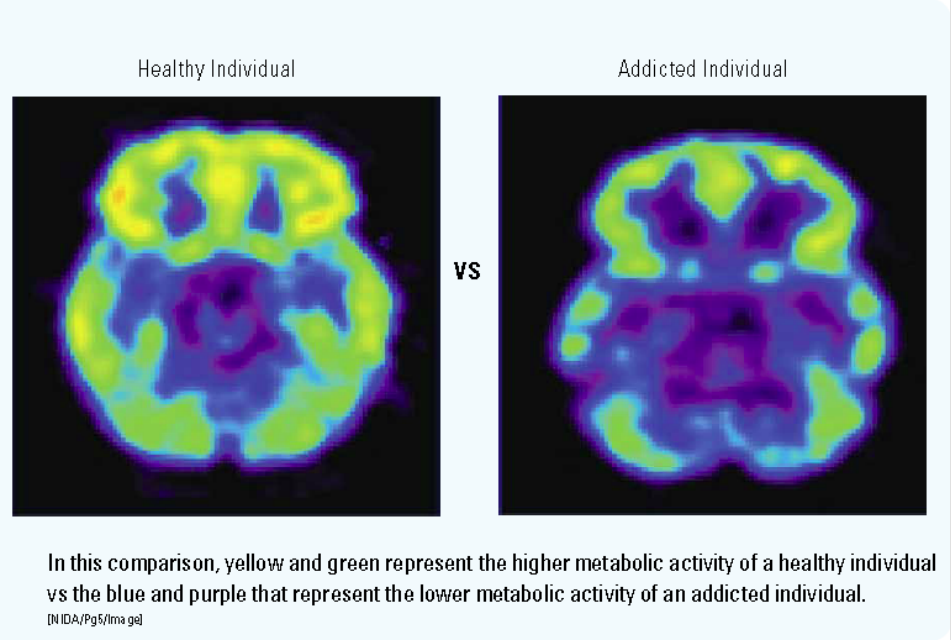
Addiction Is a Chronic, Relapsing Brain Disease

Addiction is a chronic, relapsing brain disease[1]

- Causes compulsive and destructive drug-seeking and drug-using behaviors[1]

Drug addiction alters brain structure and function

- Can be long-lasting
- Associated with problems in an abusers' cognitive and decision-making abilities[1]



1. NIDA. *NIH Pub No. 10-5605;* 2010.

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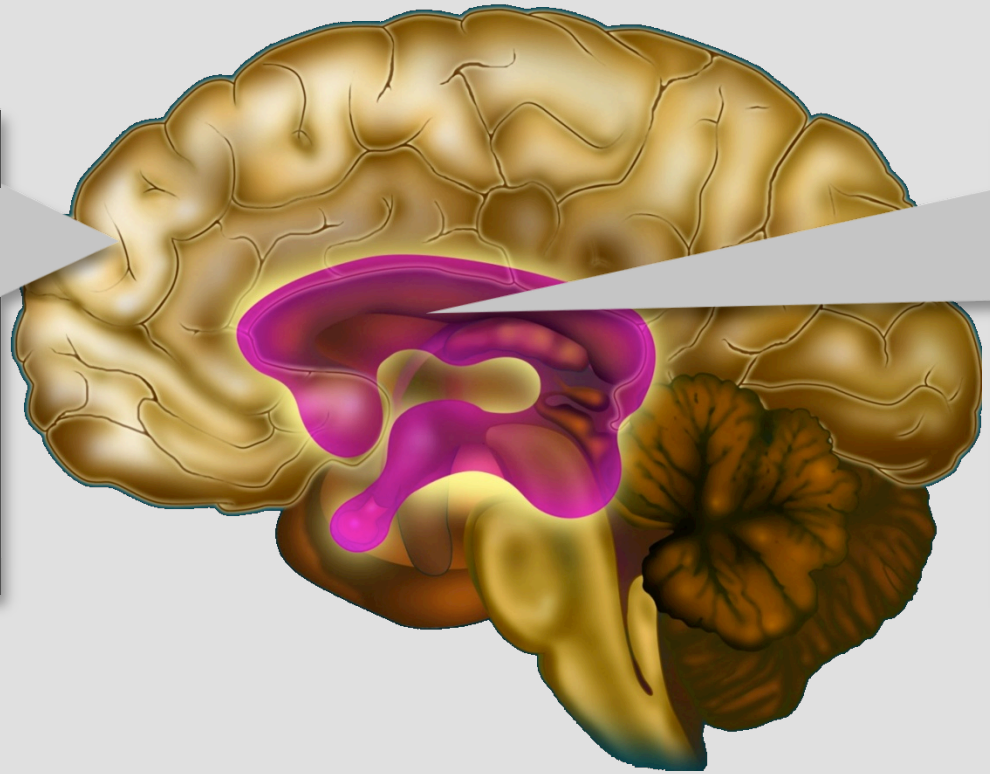
Comprehensive Treatment Improves Chances of Recovery

Addiction alters two regions of the brain[1]



CORTEX

Role[2]:

- Decision Making
- Thinking
- Reasoning
- Learning
- "Will Power"

LIMBIC REGION

Role[2]:

- Basic Drives
- Euphoria

1. NIDA. *NIH Pub No. 10-5605.* 2010. 2. Fowler JS, et al. *Sci Pract Perspect.* 2007;3(2):4–16.

DSM-IV Definition of Substance Dependence

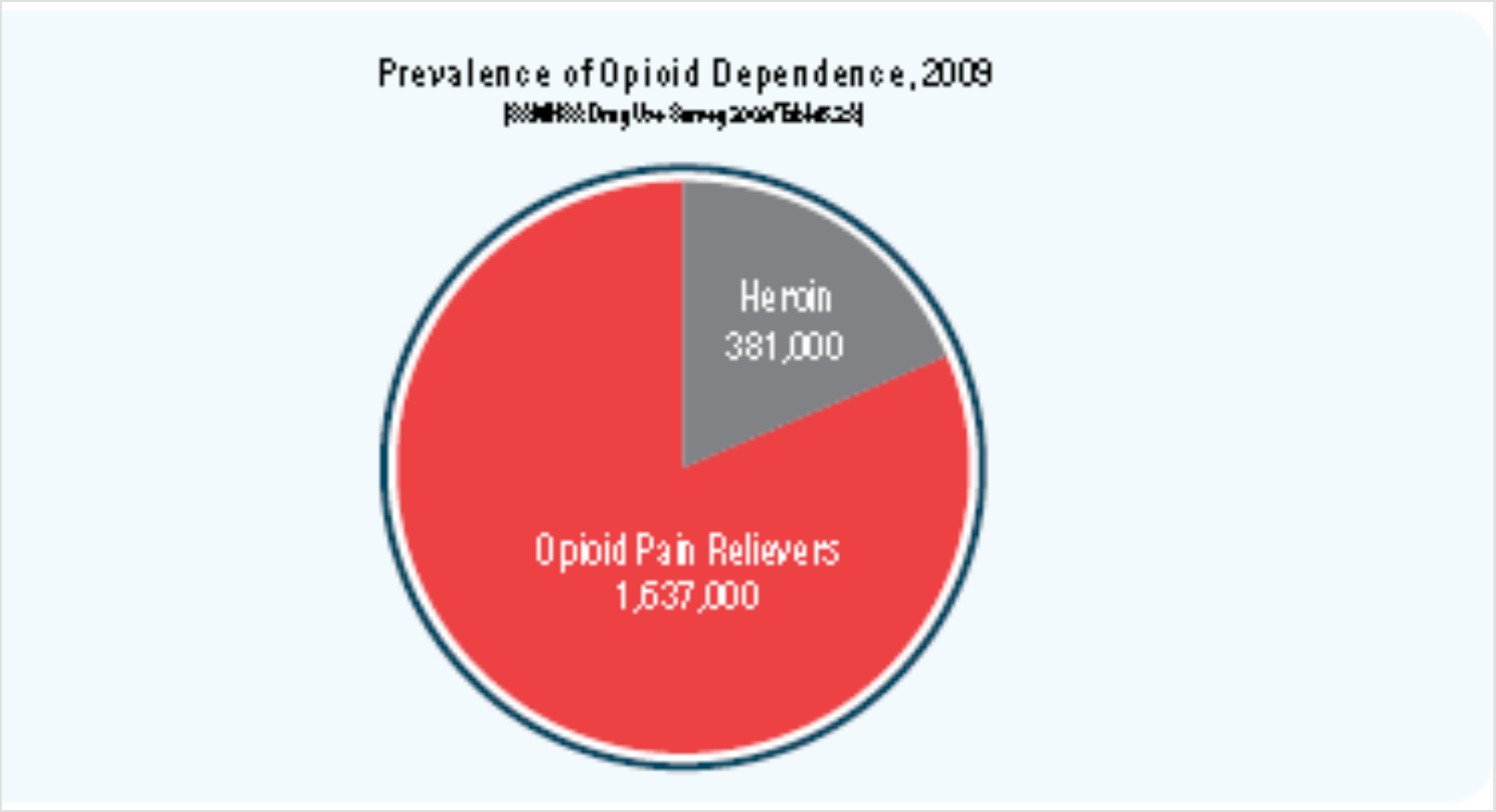
Exhibit ≥3 Symptoms in a 12-Month Period
Tolerance (marked increase in amount; marked decrease in effect)
Characteristic withdrawal symptoms; substance taken to relieve withdrawal
Substance taken in larger amount and for longer period than intended
Persistent desire or repeated unsuccessful attempts to quit
Much time/activity to obtain, use, or recover from effects
Important social, occupational, or recreational activities given up or reduced
Use continues despite knowledge of adverse consequences (e.g., failure to fulfill role obligation, use when physically hazardous)

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision;* 2000.

Prevalence of Opioid Dependence

Over 2 million people* in the US are opioid dependent

More than 80% are dependent on prescription opioid pain relievers



*Aged 18 or older, 2009

Substance Abuse and Mental Health Services Administration. Office of Applied Studies, *HHS Publication No. SMA 09-4434*; 2009.

VIVITROL®
(naltrexone for extended-release injectable suspension) 380 mg

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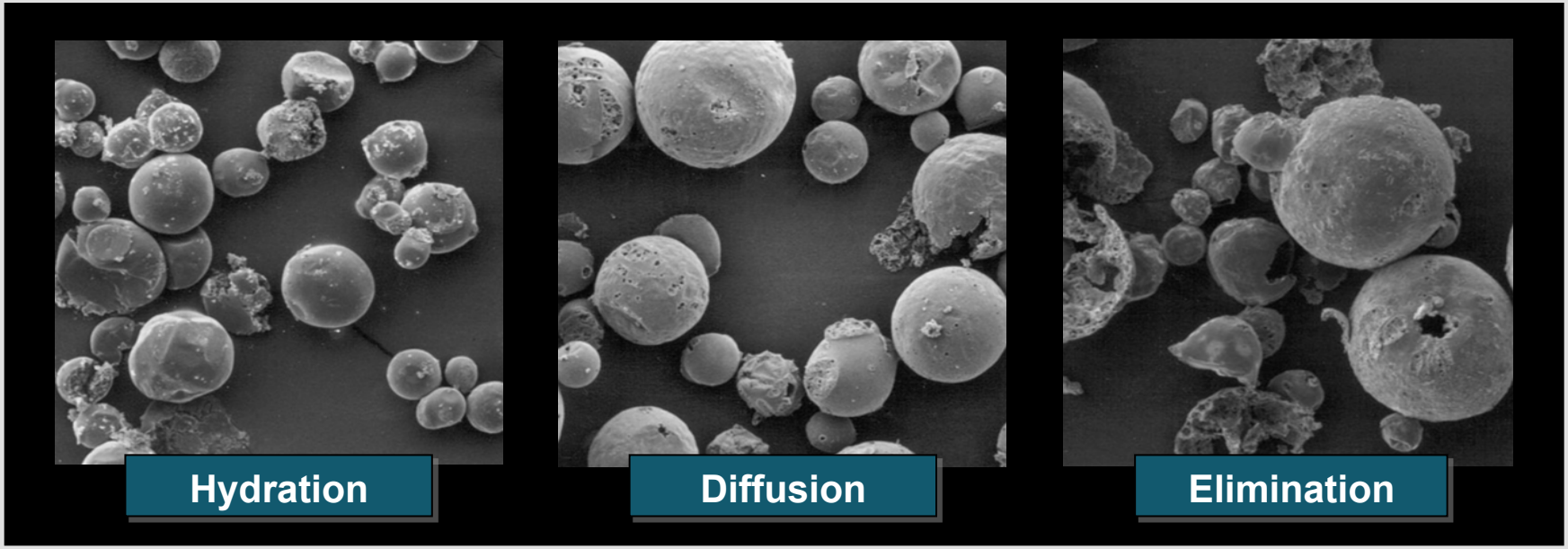
(naltrexone for extended-release injectable suspension) 380 mg/vial

Once-monthly dosing. Day by day control.

VIVITROL Microspheres



Elimination: polymer eventually metabolized and eliminated as CO_2 and H_2O

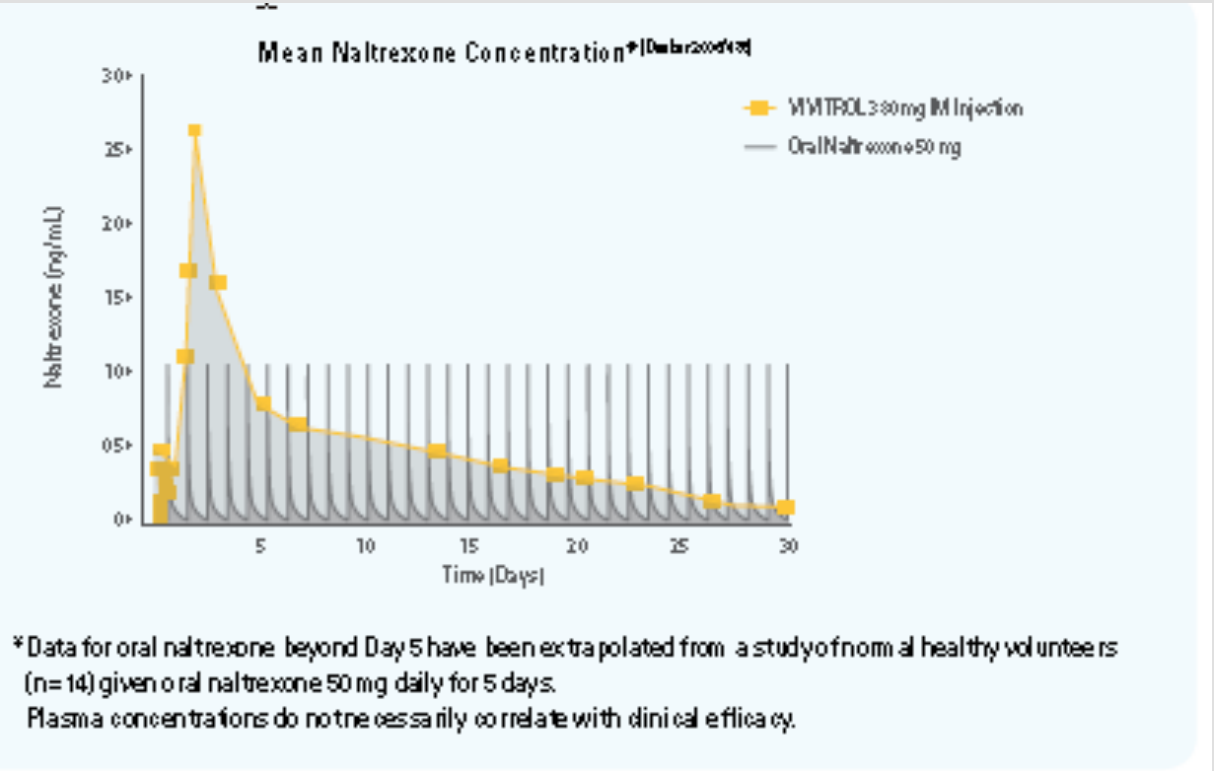
1. Dean RL. *Front Biosci*. 2005;10:643–655. 2. Data on file. Alkermes, Inc.

VIVITROL Indications and Usage

- VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL
  - Patients should not be actively drinking at the time of initial VIVITROL administration
- VIVITROL is indicated for prevention of relapse to opioid dependence, following opioid detoxification
- Opioid-dependent patients, including those being treated for alcohol dependence, must be opioid-free, for a minimum of 7 – 10 days, at the time of initial VIVITROL administration
- Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support
- VIVITROL has a boxed warning

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

VIVITROL Pharmacokinetics



*Data for oral naltrexone beyond Day 5 have been extrapolated from a study of normal healthy volunteers (n=14) given oral naltrexone 50 mg daily for 5 days.
Plasma concentrations do not necessarily correlate with clinical efficacy.

- VIVITROL delivers medication continuously over the approved dosing interval
- Maintains opioid blockade for a full 28 days
- Oral naltrexone relies on daily dosing and results in fluctuating plasma concentrations

VIVITROL provides higher cumulative plasma concentrations over 28 days † at one-fourth the dose—380 mg vs 1500 mg

- 1500 mg assumes oral naltrexone 50 mg is taken every day for 28 days

†Plasma concentrations do not necessarily correlate with clinical efficacy.

Dunbar JL et al. *Alcohol Clin Exp Res*, 2006;30(3):480–490.

Vivitrol®
(naltrexone for extended-release injectable suspension) 380 mg/vial
Once-monthly dosing. Day by day control.

Important Safety Information: 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.

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

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Important Safety Information: Contraindications

VIVITROL therapy is contraindicated in patients:

- With acute hepatitis or liver failure
- Receiving opioid analgesics
- With current physiologic opioid dependence
- In acute opioid withdrawal
- Who fail the naloxone challenge test or have a positive urine screen for opioids
- Who have previously exhibited hypersensitivity to naltrexone, polylactide co-glycolide (the polymer structure for VIVITROL microspheres), carboxymethylcellulose or any other components of the diluent

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

Clinical Trial - Study Population

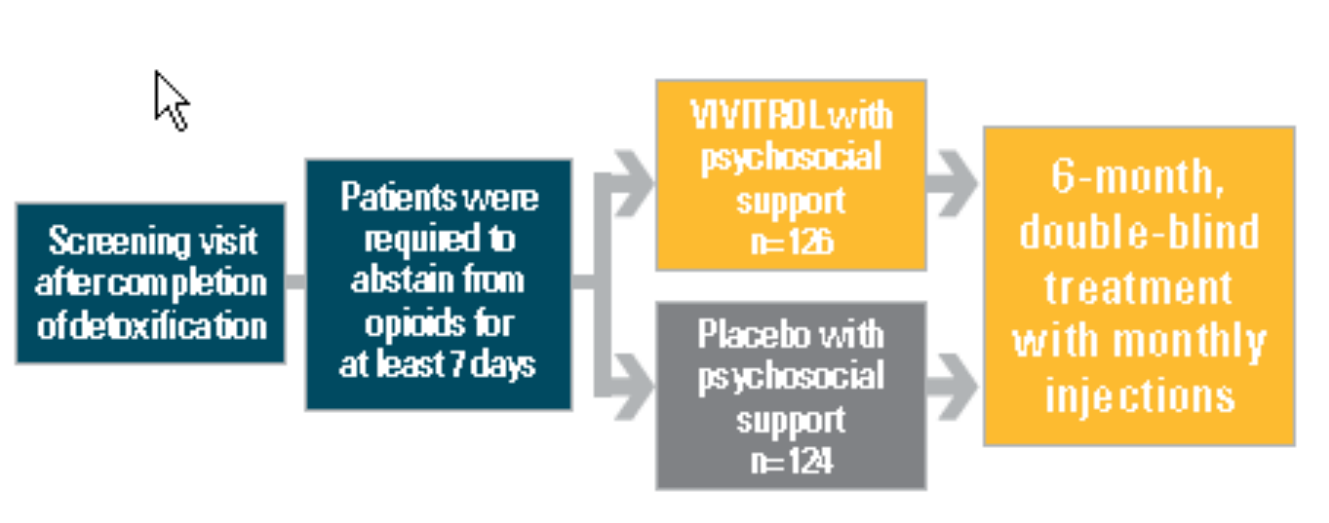
- Evaluated patients ≥18 years of age, diagnosed with opioid dependence
  - Prior to the study, participants reported using heroin (88%), methadone (12%), and other opioids/analgesics (13%)
  - Prior to treatment initiation, participants eligible for study entry were voluntarily seeking treatment, completing ≤30 days of inpatient opioid detoxification, and were not taking opioids for at least 7 days
  - Mean duration of opioid dependence among study participants was 9–10 years
  - Other baseline clinical characteristics included the presence of hepatitis C (89%) and HIV (41%)

Data on file. Alkermes, Inc. (Clinical Study Report).

Clinical Trial - Study Design

The efficacy and safety of VIVITROL were evaluated in a 24-week, multicenter, double-blind, placebo-controlled trial

- Study participants were randomized to receive VIVITROL 380 mg (n = 126) or placebo (n = 124) via IM injection every 4 weeks
- Study participants received biweekly psychosocial therapy by a trained psychologist or psychiatrist, and a weekly urine test
- Subjects provided additional self-report of opioid use
- After randomization, a 4-week period for treatment engagement was allowed



1. VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010. 2. Data on file. Alkermes, Inc. (Clinical Study Report).

Vivitrol®
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Once-monthly dosing. Day by day control.

Important Safety Information: Unintended Precipitation of Opioid Withdrawal

- To prevent occurrence of an acute withdrawal reaction in patients dependent on opioids, or exacerbation of a pre-existing subclinical abstinence syndrome:
  - Patients, including those treated for alcohol dependence, must be opioid-free for a minimum of 7–10 days before starting VIVITROL treatment.
  - Patients must be free of all opioid-containing medications, including medications used to treat opioid dependence.
- 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.

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

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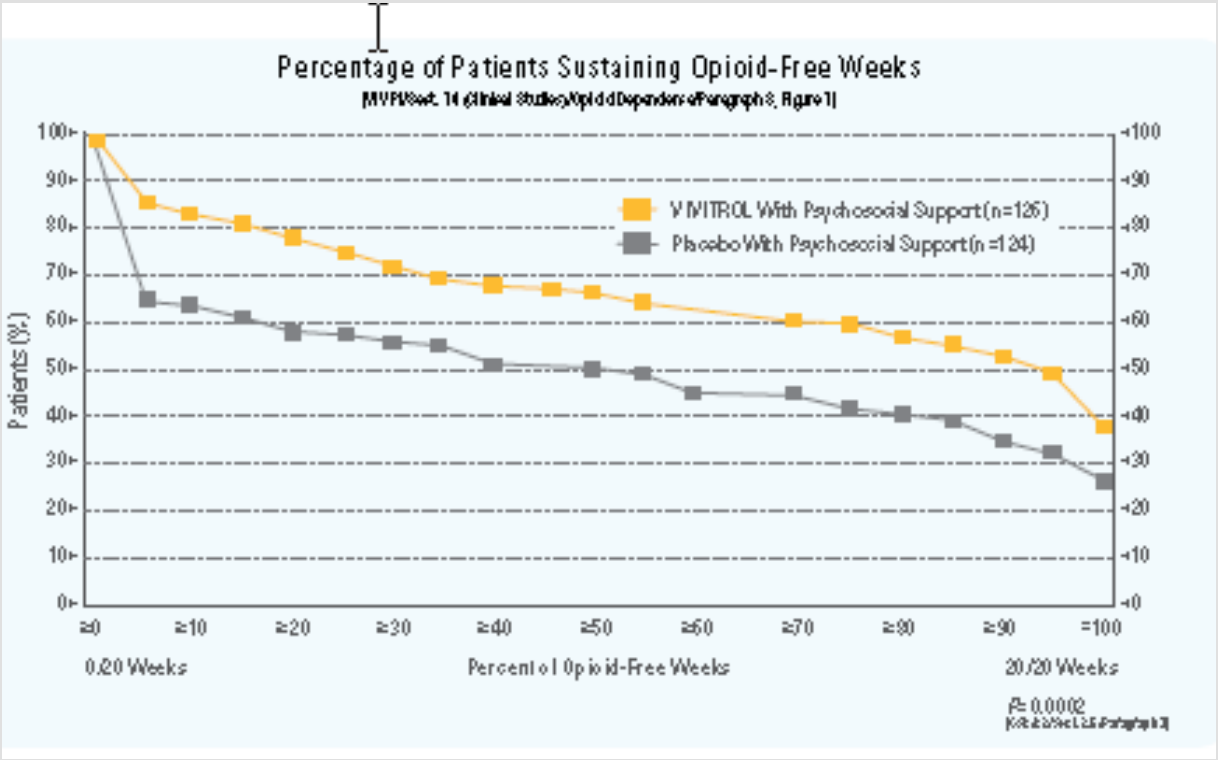
Clinical Trial - Evaluation of Efficacy and Safety in Opioid Dependence

- **Primary endpoint**
  - Cumulative percentage of patients with opioid-free weeks ranging from no visits (0%) to all visits (100%), week 5 - 24
  - Opioid free was defined as:
    1. Attend the weekly clinic visit
    2. A negative urine drug test for opioids
    3. No self-reported opioid use

Data on file. Alkermes, Inc. (Clinical Study Report).

Clinical Trial - Primary Endpoint: Opioid-Free Weeks

- Complete abstinence was achieved by 36% of the VIVITROL-treated group vs 23% of the placebo group



VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

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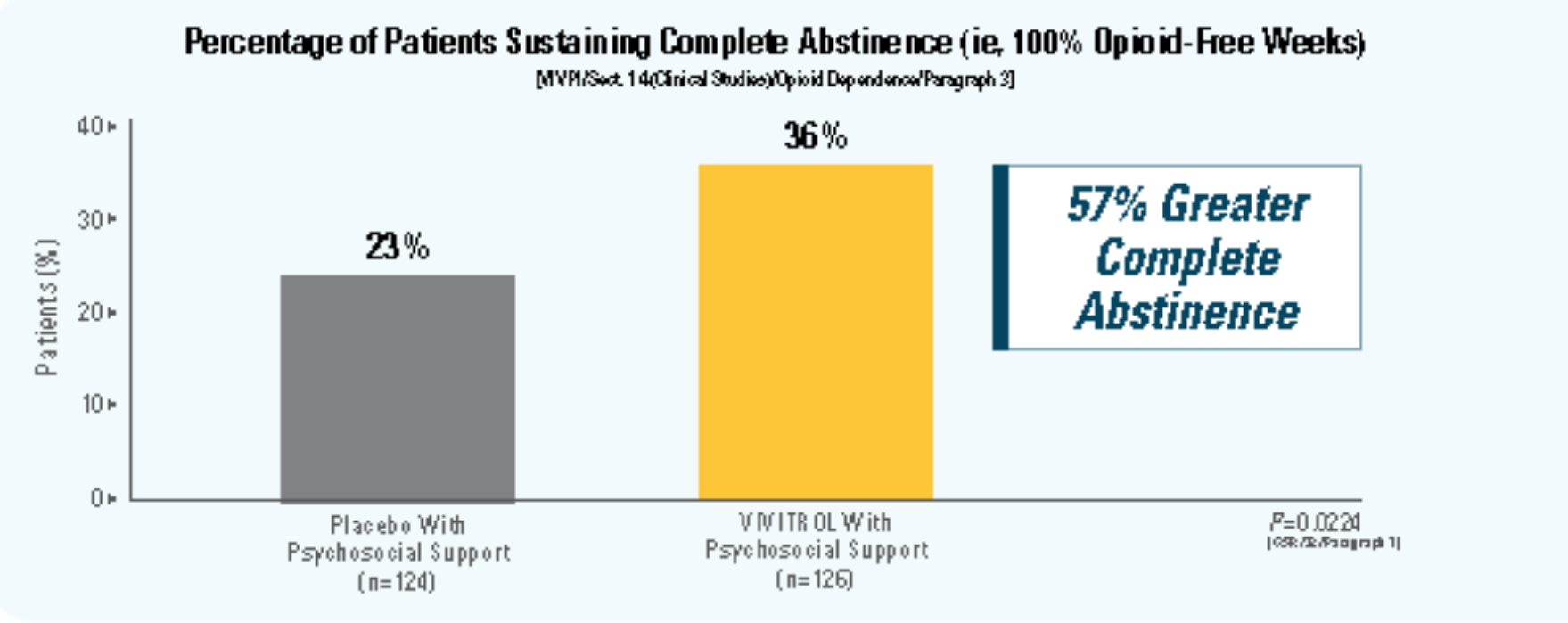
Significant Improvement in Opioid-Free Recovery With VIVITROL



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VIVITROL – Clinical Study Experience: Safety

- In the pivotal trial, VIVITROL was generally well tolerated
  - Discontinuation rates due to adverse events were the same for both treatment groups (2% in patients treated with VIVITROL and 2% in patients treated with placebo)
  - No overdose events or other severe adverse events were reported

Events That Occurred in ≥2% of Patients Treated With VIVITROL and Occurred More Frequently in the VIVITROL Group vs the Placebo Group

	VIVITROL With Psychosocial Support n=126	Placebo With Psychosocial Support n=124
Alanine aminotransferase increased	13%	6%
Aspartate aminotransferase increased	10%	2%
Gamma-glutamyltransferase increased	7%	3%
Nasopharyngitis	7%	2%
Insomnia	6%	1%
Influenza	5%	4%
Hypertension	5%	3%
Injection site pain	5%	1%
Toothache	4%	2%
Headache	3%	2%

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

VIVITROL – 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 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.

Important Safety Information: Opioid Overdose Following an Attempt to Overcome Opioid Blockade

- It is also possible for patients to overcome the opioid blockade of VIVITROL
  - Although VIVITROL is an effective antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable
  - Attempts to overcome the opioid blockade to VIVITROL may lead to potential overdose
- Family members and caregivers should be alerted to this important information

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

Important Safety Information: Reversal of VIVITROL Blockade for Pain Management

- In an emergency situation involving patients receiving VIVITROL, suggestions for pain management include:
  - Regional analgesia
  - Non-opioid analgesics
- If an opioid is required as part of anesthesia or analgesia:
  - Patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of a surgical or diagnostic procedure
- The opioid therapy must be administered by individuals specifically trained in the use of anesthetic drugs and the management of respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

Important Safety Information: Depression and Suicidality

- Opioid-dependent patients, including those taking VIVITROL, should be monitored for the development of depression or suicidal thoughts
  - Opioid- and alcohol-dependent individuals, including those taking VIVITROL, should be monitored for the symptoms of depression or suicidal thinking
  - Family members 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
  - They should be cautioned to report such symptoms to the patient's healthcare professional
- Adverse events involving depressed mood or suicidal thinking were not reported by any patient in either treatment group (VIVITROL or placebo) in the pivotal, opioid dependence trial
- Adverse events of a suicidal nature (depressed mood, suicidal ideation, suicide attempt) were reported by 5% of patients treated with VIVITROL and 10% of patients treated with oral naltrexone in an open-label, long-term safety study

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VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

Important Safety Information: Eosinophilic Pneumonia and Hypersensitivity Reactions

- Eosinophilic Pneumonia
  - Consider the diagnosis of eosinophilic pneumonia if patients develop progressive dyspnea and hypoxemia
  - Patients should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia
- Hypersensitivity Reactions Including Anaphylaxis
  - Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis
  - Patients should be advised to seek immediate medical attention in a healthcare setting prepared to treat anaphylaxis

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

Important Safety Information: Intramuscular Injections and Cross-Reactivity

- Intramuscular Injections
  - VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder
- 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

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

Directions for Use

Vivitrol®

(naltrexone for extended-release injectable suspension) 380 mg/vial

Once-monthly dosing. Day by day control.

The VIVITROL Kit

- One vial of VIVITROL microspheres
- One vial of diluent
- One 5-mL syringe
- One 1-inch 20-gauge preparation needle
- Two 1 1/2-inch 20-gauge administration needles
- Two 2-inch 20-gauge administration needles

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

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VIVITROL Storage

- VIVITROL is shipped in temperature-controlled packaging.
- VIVITROL should always be kept refrigerated and not frozen.
- Unrefrigerated, VIVITROL microspheres can be stored at temperatures not exceeding 25°C for no more than 7 cumulative days prior to administration.
- Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

VIVITROL Preparation

- VIVITROL must be prepared and administered by a healthcare professional
- Prior to administration, VIVITROL must be removed from the refrigerator for at least 45 minutes to reach room temperature
- Use the preparation needle to add the diluent to the microspheres vial
- Mix the powder and diluent by shaking the vial vigorously for approximately 1 minute
- Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit
- Do not substitute any other components for the components of the carton

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

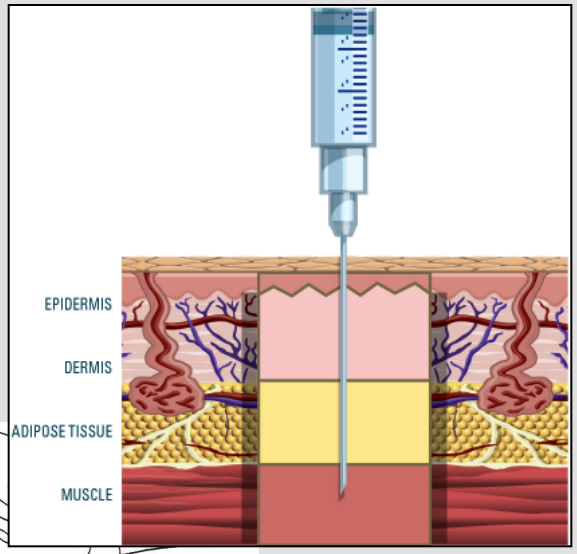
VIVITROL Preparation (continued)

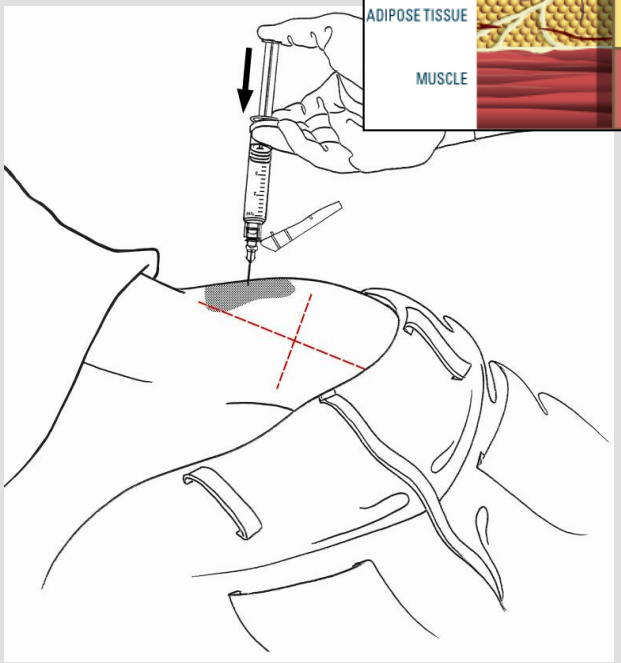
- Once the suspension has been reconstituted, it needs to be administered immediately
- Withdraw the suspension immediately into the syringe
- Replace the preparation needle with an administration needle (1 ½ inches or 2 inches) and prepare 4 mL of suspension to administer immediately by deep intramuscular (IM) injection into the upper, outer quadrant of the gluteal muscle
- After administration, dispose of used and unused items in proper waste containers

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

VIVITROL Administration

- VIVITROL is given as an IM gluteal injection every 4 weeks or once a month
  - VIVITROL should be injected into the upper, outer quadrant of the buttock, deep into the muscle
  - The buttock site of injection should be alternated each month
- VIVITROL must not be administered intravenously, subcutaneously, or in the adipose layer
- VIVITROL should be administered by a healthcare professional





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Important Safety Information: Injection Site Reactions

- VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe
- In one clinical trial, a 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 [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

Important Safety Information: Injection Site Reactions, cont.

- VIVITROL is administered as an intramuscular gluteal injection. Inadvertent subcutaneous injection of VIVITROL may increase the likelihood of severe injection site reactions
- VIVITROL must be injected using one of the two customized administration needles (1 ½ inches or 2 inches) provided. 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
- 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

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

Important Safety Information: Opioid Overdose at the End of a Dosing Interval or After Missing a Dose

- After opioid detoxification, patients are likely to have reduced tolerance to opioids
- Patients may be more sensitive to lower doses of opioids at the end of a dosing interval—near the end of the month after VIVITROL was administered, after a dose of VIVITROL is missed, or after VIVITROL treatment is discontinued
  - This could result in life-threatening opioid intoxication

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

VIVITROL Acquisition and Reimbursement

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Once-monthly dosing. Day by day control.

Touchpoints: Connecting People With Care in Recovery

Touchpoints is a comprehensive support service for VIVITROL providers and their patients

- From a single access point, Touchpoints provides reimbursement, distribution, follow-on referral, and continuity of care/adherence support

Touchpoints services include:

- Reimbursement coverage verification
- Submission of VIVITROL prescriptions to specialty pharmacies
- Co-pay assistance for eligible patients
- Access to a network of VIVITROL injection providers
- Referral and support for providers and patients transitioning between settings of care

Designed to be easy to use

- One simple enrollment form gives you and your patients free access to all that Touchpoints has to offer

Enroll at 1-800-VIVITROL (1-800-848-4876) or www.vivitrol.com

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Once-monthly dosing. Day by day control.

Enroll in Touchpoints

touchpoints℠

Connecting people with care in recovery

Patients and providers can enroll:

- 1-800-VIVITROL (1-800-848-4876)
- www.vivitrol.com

VIVITROL Reimbursement

- VIVITROL is covered by the majority of commercial and public payers.*
- As with most injectable drugs, prior authorization is typically required.
- Call 1-800-VIVITROL (1-800-848-4876) to contact Touchpoints Product Access or your local Addiction Recovery Associate for more information.

*Based on Touchpoints Enrollment benefit verification data.

Patient Co-Pay Assistance

- **$0 co-pay up to $500/ month for 13 months***
  - No financial eligibility requirement
- **Call 1-800-VIVITROL(1-800-848-4876) Option 2**

*Eligibility for Alkermes-sponsored co-pay assistance:
Offer valid for prescriptions for FDA-approved labeled indications. Patients must be at least 18. Offer not valid for prescriptions purchased under Medicaid, Medicare, or any federal or state healthcare program, including any state medical or pharmaceutical assistance program. Offer not valid in Massachusetts. Offer not valid for cash-paying patients. Void where prohibited by law, taxed, or restricted. Alkermes, Inc., reserves the right to rescind, revoke, or amend these offers without notice.

What Is VIVITROL?

VIVITROL is:

- A monthly extended-release injectable formulation of naltrexone
- Administered once monthly by a healthcare professional
- An effective supplement to psychosocial treatments
- A competitive opioid blocker (i.e., high-affinity antagonist)

VIVITROL is NOT:

- Euphorigenic (i.e., pleasure producing)
- Addictive (i.e., leading to physical dependence)
- A narcotic (i.e., a substance that meets the DEA criteria for classification as a controlled substance)

VIVITROL [full prescribing information]. Waltham, MA: Alkermes, Inc.; October 2010.

VIVITROL: Acquisition and Directions for Use Summary

- Touchpoints is a free service that provides a single access point for reimbursement, distribution, follow-on referral, continuity of care, and adherence support
  - Enroll in Touchpoints by calling 1-800-VIVITROL (1-800-848-4876) or visiting www.vivitrol.com
- VIVITROL is dispensed in a single-use kit with all the components required for use. Use only the components of the kit and do not make any substitutions
  - VIVITROL is shipped in temperature-controlled packaging and should be kept refrigerated until 45 minutes before use
- VIVITROL must be prepared and administered by a healthcare professional
  - VIVITROL is given once a month as an IM gluteal injection
- VIVITROL is covered by the majority of commercial and public payers
- A co-pay assistance program is available to eligible patients

For More Information

Contact your Addiction Recovery Associate

1-800-VIVITROL

(1-800-848-4876)

Option 3

www.vivitrol.com

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