

NALTREXONE FOR EXTENDED-RELEASE INJECTABLE SUSPENSION FOR TREATMENT OF ALCOHOL DEPENDENCE

What is naltrexone for extended-release injectable suspension?

In April 2006, the U.S. Food and Drug Administration (FDA) approved a new extended-release injectable formulation of naltrexone (Vivitrol®) for the treatment of alcohol dependence. In 1994, the FDA had approved *oral* naltrexone for treating alcohol use disorders, based on multiple clinical studies that found the medication was generally safe and significantly reduced alcohol craving, alcohol consumption, and relapse.

Table 1 provides a comparison of oral naltrexone and naltrexone for extended-release injectable suspension (injectable naltrexone).

Not surprisingly, additional studies have found that the effectiveness of oral naltrexone varied according to patient compliance with the medication regimen.¹ An extended-release preparation of naltrexone had been sought for more than 30 years, and injectable naltrexone was developed in part to help address this issue of patient nonadherence to treatment.

Table 1: Comparison of Oral Naltrexone and Extended-Release Injectable Naltrexone*

	Oral Naltrexone (ReVia®, Depade®)	Naltrexone for Extended-Release Injectable Suspension (Vivitrol®)
Mechanism of Action	Blocks brain opiate receptors, attenuates euphoria associated with alcohol use, makes alcohol use less rewarding, and reduces craving. Precise mechanism unknown.	Same as oral naltrexone; 30-day duration of action.
Usual Adult Dosage and Prescribing Information	One 50-mg tablet daily. Available by prescription from pharmacies.	380 mg given as deep intramuscular (IM) injection, once a month or every 4 weeks.† Available only to prescribing medical personnel as single-use cartons containing one 380-mg vial of naltrexone microspheres, one vial diluent, one syringe, and needles.

Table 1 continues on the next page.



Table 1: Comparison of Oral Naltrexone and Extended-Release Injectable Naltrexone (continued)*

	Oral Naltrexone (ReVia[®], Depade[®])	Naltrexone for Extended-Release Injectable Suspension (Vivitrol[®])
Examples of Drugs Causing Interactions	Opioids and medications containing opioids (naltrexone blocks the action of opioids).	Same as oral naltrexone.
Common Side Effects	Nausea, vomiting, decreased appetite, somnolence, fatigue, headache, dizziness, and anxiety.	Same as oral naltrexone, plus reaction at injection site, joint pain, muscle aches, or cramps.
Contraindications	Hypersensitivity to naltrexone. Currently using opioids or in acute opioid withdrawal. Anticipated need for opioid analgesics. Acute hepatitis or liver failure.	Same as oral naltrexone, plus sensitivity to any components of diluent, inadequate muscle mass for deep IM injection, rash, or infection at injection site.
Precautions	Other hepatic disease. Boxed warning about liver toxicity, although naltrexone does not appear to be toxic at recommended doses. Renal impairment. History of suicide attempts or depression. If opioid analgesia is required, larger doses may be needed, and respiratory depression may be deeper and more prolonged. FDA pregnancy category C.‡	Same as oral naltrexone, plus hemophilia or other bleeding problems.
Serious Adverse Reactions	Will precipitate severe withdrawal if the patient is dependent on opioids. Hepatotoxicity (although naltrexone does not appear to be a hepatotoxin at recommended doses).	Same as oral naltrexone, plus infection at the injection site, depression, and rare events including allergic pneumonia and suicidal ideation and behavior.

* Based on information in the FDA-approved product labeling or published medical literature.

† Because it is administered as an injection, naltrexone for extended-release injectable suspension may be covered as a medical benefit and is available only through specialty pharmacies. For more information, contact your specialty pharmacy provider of choice, call VIP3 (Vivitrol Information for Patients, Physicians, and Providers) at 1-800-848-4876, or visit www.vivitrol.com.

‡ FDA pregnancy category C: Animal studies have indicated potential fetal risk OR have not been conducted and no or insufficient human studies have been done. The drug should be used with pregnant or lactating women only when potential benefits justify potential risk to the fetus or infant.

How does injectable naltrexone address patient nonadherence?

Patient nonadherence is a common problem with all types of oral medications. In addition, people with substance use disorders experience fluctuations in their motivation for abstinence, further affecting their compliance with taking their medication. With injectable naltrexone, one intramuscular injection is effective for 4 weeks, reducing opportunities for patients to cease their medication.

What is the efficacy of injectable naltrexone?

The efficacy of injectable naltrexone in the treatment of alcohol dependence was evaluated in a 6-month, randomized, double-blind, multicenter trial of outpatients dependent on alcohol.² Psychosocial support in addition to medication was provided to all patients. Subjects were randomized to three groups: Vivitrol 190 mg, Vivitrol 380 mg, or placebo. Patients treated with 380 mg of injectable naltrexone in conjunction with psychosocial support had a greater reduction in the number of heavy drinking days than those treated with placebo. A subset of 53 patients (8 percent) who abstained completely from drinking in the week before the first dose of Vivitrol had greater reductions in the number of both drinking days and heavy drinking days than those patients treated with placebo. These patients were also more likely than patients treated with placebo to be completely abstinent. The same treatment effects were not seen among the subset of 571 patients (92 percent) who were actively drinking when treatment with injectable naltrexone was begun.

How safe is injectable naltrexone?

Before FDA approval, injectable naltrexone was studied in more than 900 patients.³ Injectable naltrexone appears to be generally well tolerated, and adverse effects tend to be mild.^{2, 4} Patients using injectable naltrexone do not develop tolerance for or dependence on the medication.

Like oral naltrexone, injectable naltrexone has a boxed warning on its packaging regarding the possibility of serious injury to those with active liver disease. However,

the warning includes the statement that naltrexone does not appear to be a hepatotoxin at recommended doses. At least one study found it to be safe for use by patients with mild to moderate liver impairment.⁵ Nonetheless, liver function should be monitored during treatment with injectable naltrexone.

Naltrexone is an opioid antagonist; to avoid serious withdrawal reactions, prescribers must ensure (through urine screens and/or a naloxone challenge test) that patients have been free of all opioid or opioid-containing medications for at least 7 days before administering injectable naltrexone. Patients with opioid use disorders also may be tempted to try to overcome the opioid-blocking effects of naltrexone by taking large amounts of opioids. Taking these large amounts of opioids is dangerous and may lead to serious injury, coma, or death.³ Patients who have taken opioid drugs or medicines before starting treatment with injectable naltrexone may possibly lose their tolerance for opioids and may respond to doses of opioids lower than those previously used. This could result in potentially life-threatening opioid intoxication. In addition, patients requiring opioids for pain management during treatment with injectable naltrexone may need an amount of opioid that is greater than usual, and the resulting respiratory depression may be deeper and more prolonged. Substance abuse specialty treatment providers should caution patients to tell physicians, dentists, and other medical professionals that they are being or have been treated with injectable naltrexone whenever an opioid analgesic might be indicated.

How can substance abuse specialty treatment providers incorporate injectable naltrexone?

Medications for alcohol use disorders do not replace counseling. Treatment with naltrexone for extended-release injectable suspension can be one part of a comprehensive management program that includes psychosocial support and participating in 12-Step or other mutual-help group programs.

If the treatment provider and patient decide that medication may help, the patient should be referred to a medical professional who can prescribe or administer it. The prescribing professional should assess the patient's medical appropriateness for therapy with injectable naltrexone by conducting a medical examination, which may include tests to rule out opioid dependence, severe liver disease, or pregnancy. Injectable naltrexone should be administered only by a medical professional (e.g., physician, nurse, physician's assistant) and is available only through specialty pharmacies. If the treatment team and patient decide that injectable naltrexone is a good choice for that patient, more information can be obtained by calling the distributor's Vivitrol information line, 1-800-848-4876.

Regular communication between substance abuse specialty treatment providers and the prescribing medical professional is essential. In particular, treatment providers need to communicate information concerning—

- Patient's reported or detected drinking or drug use episodes;
- Patient's concerns about side effects;
- Issues affecting the patient's safety (suicidal ideation, reported or observed increase in levels of depression or anxiety, or significant physical complaints); and
- Patient's expressed desire to stop taking the medication.

Substance abuse specialty treatment providers should encourage patients to talk directly to their prescribing professionals about these and other issues or questions they may have.

When determining how long a patient should continue on injectable naltrexone therapy, an individualized assessment by the prescribing professional and treatment team, with input from the patient, is best to determine the optimal length of time for medication treatment. Controlled studies have been conducted for up to 6 months; some patients have been treated with injectable naltrexone therapy for a year or longer.

What To Tell the Patient

Substance abuse specialty treatment program staff can support patients taking injectable naltrexone by educating them about the drug, including—

- Informing patients about the potential benefits of the medication;
- Ensuring that patients understand that medications for alcohol dependence do not replace counseling and that treatment with injectable naltrexone should be part of a comprehensive treatment and recovery program that includes psychosocial support and participating in 12-Step or other mutual-help group programs;
- Ensuring that patients understand that they will need to get an injection once a month or every 4 weeks;
- Encouraging patients to talk to their prescribing professional about how long to continue therapy with injectable naltrexone;
- Encouraging patients to talk to their prescribing professional about all other prescription and nonprescription medications they are taking;
- Encouraging patients to promptly report side effects (including injection site reactions that do not improve over time, shortness of breath or difficulty breathing, overwhelming sadness or suicidal ideation, abdominal pain, yellowing of the skin or eyes, or change in color of urine or stools) to their prescribing professional;
- Encouraging women to inform all their prescribing professionals immediately if they become pregnant during therapy;
- Advising patients to continue taking the medication if a slip or relapse occurs and to inform their counselors and prescribing professionals immediately;
- Reminding patients to inform physicians or dentists of current or previous treatment with injectable naltrexone whenever an opioid analgesic for pain management might be indicated; and
- Encouraging patients to carry a medication alert card or wear a medical alert bracelet or tag indicating that they are receiving treatment with injectable naltrexone.

Notes

1. Mann, K. (2004). Pharmacotherapy of alcohol dependence: A review of the clinical data. *CNS Drugs*, 18(8), 485–504.
2. Garbutt, J. C., Kranzler, H. R., O'Malley, S. S., Gastfriend, D. R., Pettinati, H. M., Silverman, B. L., et al. (2005). Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *JAMA*, 293(13), 1617–1625.
3. Vivitrol prescribing information, Alkermes, Inc., www.vivitrol.com.
4. Kranzler, H. R., Wesson, D. R., & Billot, L. (2004). Naltrexone depot for treatment of alcohol dependence: A multicenter, randomized, placebo-controlled clinical trial. *Alcoholism: Clinical and Experimental Research*, 28(7), 1051–1059.
5. Turncliff, R. Z., Dunar, J. L., Dong, Q., Silverman, B. L., Ehrich, E. W., Dilzer, S. C., et al. (2005). Pharmacokinetics of long-acting naltrexone in subjects with mild to moderate hepatic impairment. *Journal of Clinical Pharmacology*, 45, 1259–1267.

Resources for Additional Information

Substance Abuse and Mental Health Services Administration (SAMHSA)

1 Choke Cherry Road, Room 8-1054
Rockville, MD 20857
Phone: 1-240-276-2130 (Office of Communications)
Web: www.samhsa.gov

SAMHSA's National Clearinghouse for Alcohol and Drug Information

Phone: 1-800-729-6686
Español: 1-877-767-8432
TDD: 1-800-487-4889
Web: www.ncadi.samhsa.gov

National Institute on Alcohol Abuse and Alcoholism
5635 Fishers Lane, MSC 9304
Bethesda, MD 20892-9304
Web: www.niaaa.nih.gov

U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-0001
Phone: 1-888-INFO-FDA (1-888-463-6332)
Web: www.fda.gov

Selected Publications

Center for Substance Abuse Treatment. (1998). *Naltrexone and Alcoholism Treatment*. Treatment Improvement Protocol (TIP) Series 28. DHHS Publication No. (SMA) 98-3206. Rockville, MD: Substance Abuse and Mental Health Services Administration. (Available through NCADI and at www.kap.samhsa.gov.)

Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration. (2005). *Acamprosate: A new medication for alcohol use disorders*. *Substance Abuse Treatment Advisory*, 4(1), Fall. (Available through NCADI and at www.kap.samhsa.gov.)

Center for Substance Abuse Treatment. (2006). *Detoxification and Substance Abuse Treatment*. Treatment Improvement Protocol (TIP) Series 45. DHHS Publication No. (SMA) 06-4131. Rockville, MD: Substance Abuse and Mental Health Services Administration. (Available through NCADI and at www.kap.samhsa.gov.)

National Institute on Alcohol Abuse and Alcoholism. (2005). *Helping Patients Who Drink Too Much: A Clinician's Guide*. Bethesda, MD: National Institutes of Health. (Available at www.niaaa.nih.gov.)

National Institute on Alcohol Abuse and Alcoholism. (2005). *A Pocket Guide for Alcohol Screening and Brief Intervention*. Bethesda, MD: National Institutes of Health. (Available at www.niaaa.nih.gov.)



Substance Abuse Treatment Advisory

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