**DESCRIPTION**

Naltrexone is an opioid antagonist that binds to the opioid receptors, blocking the euphoric effects of exogenous opioids in those who are opioid dependent. This document addresses the extended-release injectable (intramuscular), long acting form of naltrexone (Vivitrol, Alkermes, Inc., Cambridge, MA). Active ingredient: naltrexone. Inactive ingredients: polylactide-co-glycolide (PLG) Diluent ingredients: carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection.

**BACKGROUND**

Medications should be prescribed as part of a comprehensive treatment approach that includes counseling and other behavioral health therapies (through existing treatment or referral to outpatient, intensive outpatient or residential treatment for substance use disorders and potentially co-occurring treatment with a psychiatrist, psychologist, or professional counselor) and/or social supports (through participation in Alcoholics Anonymous and other mutual-help programs). Medication-Assisted Treatment (MAT) is the use of pharmacological interventions in combination with counseling and behavioral therapies to provide a client-centered and whole-person approach to substance used disorder (SUD) treatment. It is the best practice for the treatment of most chronic conditions that require both pharmacologic and lifestyle behavioral interventions (e.g., diabetes, addiction). Certain people find it difficult to comply with daily dosing regimens and have been known to miss days of dosing which could result in relapse.

Vivitrol is an extended release formulation of naltrexone, which has been found to be effective in the treatment of alcohol and opioid dependence and is most effective when used in combination with medication and behavioral therapies. Extended-release injectable naltrexone is approved for use only in persons who can refrain from drinking or opioid use for several days before treatment begins—a subgroup of the patient population in whom efficacy has been demonstrated. Behavioral treatment emphasizes support of abstinence, including participation in group therapy stressing motivational enhancement, trauma-informed treatment, relapse prevention skills, and compliance with the medication regimen. Therapy is customized to client needs and there is benefit from a synergism than what supportive and coping skills therapy might offer individually. The table below summarizes Vivitrol benefits.

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| --- | --- | --- |
| **Benefits** | **Treatment Effects****(decrease)** | **Treatment Outcomes (improved)** |
| Prescribed/monitored by a medical professional | Cravings | Success rates in the first six (6) months of recovery |
| FDA-approved | Drug-related deaths | Treatment retention |
| Regulated potency | Risk of relapse on alcohol /opioid use | Likelihood of abstinence |
| Curbs cravings and withdrawals | Total number of drinking days | Employment rates |
| Benefits outweigh risks | Criminal activities |  |

**DEFINITIONS**

*Agonist:* A drug that binds to a receptor of a cell and triggers a response by the cell. An agonist often mimics the action of a naturally occurring substance.

*Antagonist:* A substance that tends to nullify the action of another, as a drug that binds to a cell receptor without eliciting a biological response, blocking binding of substances that could elicit such responses.

*Endogenous:* Originating or produced within the body.

*Exogenous:* Originating from outside the body; derived externally.

*First-pass hepatic metabolism:* When an oral medication undergoes passage through the gut and liver before reaching the systemic circulation; the concept provides information about the therapeutic effect of an orally administered drug versus administration via intramuscular or intravenous injection.

*Naloxone Challenge Test:* A test in which naloxone is administered to verify current opioid dependence. Withdrawal symptoms evoked by naloxone's antagonist interaction with opioids confirm an individual's current dependence.

**CLINICAL INDICATIONS/MEDICAL NECESSITY**

**Alcohol Dependence**

In people with alcohol dependence, it is believed that this blockade (opioid antagonism) diminishes craving for alcohol and leads to a greater ability to resist urges to drink excessively. Naltrexone is available in two forms: oral daily form (ReVia®, Depade®) and injectable monthly extended-release form (Vivitrol®). The latter was approved by FDA for treatment of alcohol dependence in 2006. Although the mechanism responsible for the reduction in alcohol consumption observed with treatment is not entirely understood, preclinical data suggests that occupation of the opioid receptors results in the blockade of the neurotransmitters in the brain that are believed to be involved with alcohol dependence. This blockade may result in the reduction in alcohol consumption observed in people treated with naltrexone.

Injectable naltrexone (Vivitrol) is considered medically necessary for the treatment of alcohol dependence when the individual:

* Is being treated for alcohol dependence; AND
* Is able to abstain from alcohol for at least 4 days in any setting prior to treatment initiation; AND
* Is not actively drinking at the time of initial injectable naltrexone (Vivitrol) administration; AND
* Actively participates in a comprehensive rehabilitation program that includes psychosocial support; AND
* Is not:
	+ Currently on opioid analgesics; OR
	+ Physiologically dependent on opioids; OR
	+ Currently in acute opioid withdrawal; AND
* Does not have:
	+ A positive urine screen for opioids; OR
	+ A failed naloxone challenge test; OR
	+ Acute hepatitis; OR
	+ Liver failure; OR
	+ Positive pregnancy test; OR
	+ Previous hypersensitivity to naltrexone, 75:25 polyactide-co-glycolide (PLG), carboxymethylcellulose or any other component of the diluent.

**Opioid Dependence**

Naltrexone is a non-opioid medication that is approved for the treatment of opioid dependence. Naltrexone is an opioid receptor antagonist; it binds to opioid receptors, but instead of activating the receptors, it effectively blocks them. Through this action, it prevents opioid receptors from being activated by agonist compounds, such as heroin or prescription pain killers, and is reported to reduce craving and prevent relapse. As opposed to other medications used for opioid dependence (methadone and buprenorphine), naltrexone can be prescribed by any individual who is licensed to prescribe medicine (e.g., physician, doctor of osteopathic medicine, physician assistant, and nurse practitioner). Both the oral daily form and the monthly injectable monthly extended-release form (Vivitrol®) are FDA approved for treatment of opioid dependence. Vivitrol® was approved by FDA for this indication in 2010.

Injectable naltrexone (Vivitrol) is considered medically necessary for the prevention of relapse to opioid dependence following detoxification when the individual:

* Is being treated for opioid dependence; AND
* Has successfully completed an opioid detoxification program; AND
* Has been opioid-free (including buprenorphine and methadone) for at least 4 days prior to initiating treatment with naltrexone (Vivitrol) injection; AND
* Actively participates in a comprehensive rehabilitation program that includes psychosocial support; AND
* Is not:
	+ Currently on opioid analgesics for pain management; OR
	+ Currently in acute opioid withdrawal; AND
* Does not have:
	+ A positive urine screen for opioids; OR
	+ A failed naloxone challenge test; OR
	+ Acute hepatitis; OR
	+ Liver failure; OR
	+ Positive pregnancy test; OR
	+ Previous hypersensitivity to naltrexone, 75:25 polyactide-co-glycolide (PLG), carboxymethylcellulose or any other component of the diluent.

**No Clinical Indication/Not Medically Necessary**

Injectable naltrexone (Vivitrol) is considered not medically necessary for the treatment of alcohol dependence or opioid dependence when the criteria above are not met. Injectable naltrexone (Vivitrol) is considered not medically necessary for the treatment of diagnoses other than alcohol dependence and opioid dependence

**CLINICAL ASSESSMENT**

Consensus opinion is that an assessment should include a medical and psychiatric history, a substance use history, and an evaluation of family and psychosocial supports. Assess the client for the following before Vivitrol is prescribed or administered.

**Clinical History**

* Liver problems
* Use or abuse street (illegal) drugs
* Hemophilia or other bleeding problems
* Kidney problems
* Other medical conditions
* Pregnant or plan to become pregnant. It is not known if Vivitrol will harm unborn baby.
* It is not known if Vivitrol passes into breastmilk and if it can harm the baby. Naltrexone (Vivitrol) is considered L1 (safest category) for lactation. While the manufacturers of Vivitrol do not recommend its use in pregnancy it is up to the clinical judgment of the provider and should be discussed with the client and informed consent obtained. If small amounts of Naltrexone are passed into the breastmilk, it should not cause any ill effects on the infant if the infant is not being administered opiates.

**Laboratory Tests**

* Initial Injection: urinalysis required and prescribing provider can initiate treatment based on clinical judgment.
* Subsequent Injections: complete a comprehensive metabolic panel to assess hepatic and renal functioning, urine drug screen just prior to injection.

**Screening**

As part of the clinical assessment, the Brief Addiction Monitor (BAM) is administered prior to the initiation of Vivitrol. The BAM provides measurement of addiction problem severity to support treatment in SUD care settings.

* Administer as a clinical interview; typically takes about 5 minutes to complete.
* Retrospectively examines the client’s behavior in the past 30-days.
* Includes items that assess Risk factors for substance use, Protective factors that support sobriety, and drug and alcohol Use.
* Produces composite scores for Risk and Protection as well as a Use score. A client's clinical status may be assessed by examining individual BAM items and/or composite scores.

**Care Management**

* ***Client receiving more than 3 consecutive doses.*** Any client exceeding three (3) consecutive doses within 90 days should have a more thorough assessment and the Substance Use Disorder team needs to have a strong clinical justification as to why **Program C** would need to continue services at that same level. For SAPC clients, approval must be obtained for injections exceeding three (3) beyond 90 days.
* ***Continuity of care.*** In a case where it is determined that Vivitrol treatment for any particular client should be discontinued, a case conference should be scheduled to discuss the treatment plan for that client including linkage to aftercare/continued treatment (i.e., discharge from residential to community care).
* ***Documentation.*** For any client receiving Vivitrol treatment who is also receiving other residential or outpatient services at **Program C**, staff will ensure that documentation in the Vivitrol medical record is included in the client’s chart.
* ***Additional Details.*** See **Program C** Policy and Procedure: Medication-Assisted Therapy.

**PRESCRIBING**

Naltrexone can be prescribed by any healthcare provider who is licensed to prescribe medications. Special training is not required; the medication can be administered in Opioid treatment program (OTP) clinics. Practitioners in community health centers or private office settings can also prescribe it for purchase at the pharmacy.

**How taken**: Intramuscular injection once every 4 weeks.

**How supplied:** Single-use carton containing 380 mg vial of Vivitrol microspheres, 4 mL vial of diluent, 5 mL syringe, 20-gauge ½-inch needle, and two 20-gauge 1½-inch needles.

**ADVERSE EVENTS AND WARNINGS**

Naltrexone generally is well tolerated, although it has the potential to precipitate severe opioid withdrawal in patients who are opioid dependent. Warnings and precautions from the FDA Product Information Label include the following:

* Vivitrol must not be administered intravenously or subcutaneously.
* Vulnerability to opioid overdose: After opioid detoxification, individuals are likely to have reduced tolerance to opioids. Vivitrol blocks the effects of exogenous opioids for approximately 28 days after administration. 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 an individual to overcome the blockade produced by Vivitrol by taking opioids is very dangerous and may lead to fatal overdose.
* Hepatotoxicity: Cases of hepatitis and clinically significant liver dysfunction were observed in association with Vivitrol exposure. Transient, asymptomatic hepatic transaminase elevations were also observed. Use of Vivitrol should be discontinued in the event of symptoms or signs of acute hepatitis.
* 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. 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.
* Eosinophilic pneumonia: Vivitrol individuals should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia.
* Hypersensitivity: Individuals should be warned of the risk of hypersensitivity reactions, including anaphylaxis.
* Precipitation of Opioid Withdrawal: Opioid-dependent and opioid-using individuals, including those being treated for alcohol dependence, should be opioid-free before starting Vivitrol treatment. An opioid-free duration of a minimum of 7-14 days is recommended for individuals to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization. Clients who have been on long-acting opiates such as Methadone and Buprenorphine will need to be off of these medications for 14 days prior to administration of Vivitrol.
* Depression and Suicidality: Vivitrol individuals should be monitored for the development of depression or suicidal thinking.
* Intramuscular Injections: Vivitrol should be administered with caution to individuals with thrombocytopenia or any coagulation disorder (e.g., hemophilia and severe hepatic failure).
* When Reversal of Vivitrol Blockade Is Required for Pain Management: In an emergency situation in individuals receiving Vivitrol, suggestions for pain management include regional analgesia or use of non-opioid analgesics. Individuals will be given a bracelet to wear in case of emergencies so that emergency personnel are aware that the client has an opiate blockade and will require higher doses of opiates to overcome the blockade with subsequent respiratory monitoring and support.

**COVERAGE**

Naltrexone long-acting injection (Vivitrol) is a covered benefit of the Medi-Cal program and is available to all Medi-Cal beneficiaries who demonstrate a medical necessity for the use of the drug. In the treatment of alcohol dependence, the injectable form of naltrexone is used in professionally supervised treatment that includes medical examination and supervision, indicated laboratory tests, psychosocial support, urinalyses, drug-use monitoring and other appropriate support such as that provided through the Drug/Medi-Cal program. Prior to initiation of treatment with naltrexone, clients must be able to abstain from alcohol in any setting, and clients should not be actively drinking at the time of initial naltrexone administration. It may be billed as either a medical claim (for all Medi-Cal beneficiaries) or a pharmacy claim (for select populations only, as indicated below). The policy for naltrexone long-acting injection, when provided as a medical benefit, can be found in the Injections: Drugs N – R section of the Medi-Cal Part 2 provider manual. It may also be available as a pharmacy benefit to Medi-Cal beneficiaries meeting both of the following criteria:

1. Charged with, or convicted of, a felony or misdemeanor; and
2. Monitored for compliance with terms and conditions of county or state supervision (including but not limited to probation, parole, 1210 PC, mandatory supervision, post-release community supervision or pretrial release), including substance abuse monitoring.

Naltrexone long-acting injection always requires a Treatment Authorization Request (TAR) and may be obtained and billed only through the specialty pharmacy network. Medi-Cal also covers the following medications for the treatment of alcohol and opioid dependence and/or prevention of relapse: acamprosate, buprenorphine, buprenorphine/naloxone, disulfiram and oral naltrexone (a TAR is required for all but disulfiram and oral naltrexone). Opioid agonist treatment with methadone is available within an opioid treatment program.

**CODING**

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply coverage. Refer to the client’s coverage in effect at the time of service to determine coverage or non-coverage of these services as it applies to the individual.

HCPCS

J2315 Injection, naltrexone, depot form, 1 mg [Vivitrol®]

ICD-9 Diagnosis [For dates of service prior to 10/01/2015]

291.0-291.9 Alcohol induced mental disorders

292.0-292.9 Drug-induced mental disorders

303.00-303.03 Acute alcoholic intoxication

303.90-303.93 Other and unspecified alcohol dependence

304.00-304.03 Drug dependence; opioid type dependence

304.70-304.73 Drug dependence, combinations of opioid type drug with any other

V11.3 Personal history of mental disorder; alcoholism

ICD-10 Diagnosis [For dates of service on or after 10/01/2015]

F10.20-F10.29 Alcohol dependence

F11.20-F11.29 Opioid dependence

Z71.41 Alcohol abuse counseling and surveillance of alcoholic

**REFERENCES**

1. American Association for the Treatment of Opioid Dependence. AATOD Guidelines for Using Naltrexone (Vivitrol) in OTPs. <http://www.aatod.org/policies/policy-statements/aatod-guidelines-for-using-naltrexone-vivitrol-in-otps/>. Accessed April 3, 2015.
2. Anthem Guideline #: CG-DRUG-21. Subject: Naltrexone (Vivitrol®) Injections for the Treatment of Alcohol and Opioid Dependence Current Effective Date: 04/15/2014.
3. National Institutes of Health (NIH) National Institute on Alcohol Abuse and Alcoholism (NIAAA): Naltrexone or specialized alcohol counseling an effective treatment for alcohol dependence when delivered with medical management. Available at: <http://www.nih.gov/news/pr/may2006/niaaa-02.htm>. Accessed on April 3, 2015.
4. Substance Abuse and Mental Health Services Administration (SAMHSA) Medication-Assisted Treatment for Substance Use. Available at: <http://www.dpt.samhsa.gov/medications/naltrexone.aspx>. Accessed on April 3, 2015.
5. Substance Abuse and Mental Health Services Administration and National Institute on Alcohol Abuse and Alcoholism, Medication for the Treatment of Alcohol Use Disorder: A Brief Guide. HHS Publication No. (SMA) 15-4907. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015.
6. Tsai, G. Medication-Assisted Treatment: Overview and Evidence. UCLA-SAPC Lecture Series. March 23, 2015.