**Name of Policy:**
Naltrexone (Vivitrol®) Injections

Policy #: 457  
Latest Review Date: December 2010  
Category: Pharmacology  
Policy Grade: B

**Background/Definitions:**
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Alcohol dependence can be treated by rehabilitation and medication. In some cases, oral medication does not achieve optimum therapeutic effect and in some cases this may be related to poor compliance in taking an oral drug. An injectable (intramuscular), long-acting form of naltrexone (Vivitrol®) has been approved by the FDA for use when the desired clinical effect is not attained with oral medication. Naltrexone is a pure opioid antagonist. It is not associated with the development of tolerance or dependence. Occupation of opioid receptors by naltrexone may block the effects of endogenous opioid peptides. The neurobiological mechanisms responsible for the reduction in alcohol consumption observed in alcohol-dependent patients treated with naltrexone are not entirely understood. However, preclinical data suggests the involvement of the endogenous opioid system.

Long term treatment for opioid dependence can take many forms, including abstinence-based treatment, opioid antagonist treatment (naltrexone), or maintenance with opioid agonists (methadone or buprenorphine or heroin administered in a controlled setting).

Naltrexone has been used to treat chronic opioid abusers, but may cause immediate withdrawal symptoms if administered prior to detoxification. Naltrexone maintenance is most effective in highly motivated patients who are closely supervised. Depot administration may be useful in cases where non-adherence to daily dosing impedes effectiveness.

Vivitrol™ is an extended release, microsphere formulation of naltrexone designed to be administered by intramuscular (IM) gluteal injection every four (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 two (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 one (1) month. Vivitrol® is FDA approved for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to the initiation of treatment, and as part of a comprehensive management program that includes psychosocial support.

Vivitrol® is also FDA approved to treat and prevent relapse after patients with opioid dependence have undergone detoxification treatment. Patients must not have any opioids in their system when they start taking the Vivitrol®.

**Policy:**
*Effective for dates of service on or after December 10, 2010:*
Injectable naltrexone (Vivitrol®) is medically necessary for the treatment of alcohol dependence when the individual:
- Is being treated for alcohol dependence; AND
- Has had an initial response and tolerates oral naltrexone (Revia®) but is unable to comply with daily dosing; AND
- Is able to abstain from alcohol for at least 7 days in an outpatient setting prior to treatment initiation; AND
• Is not actively drinking at the time of initial Vivitrol® administration.

Injectable naltrexone (Vivitrol®) is medically necessary for the treatment of and to prevent the relapse of opioid dependence when the individual:

• Has undergone detoxification treatment; AND
• Does not have any opioids in his system at the time of initial Vivitrol® administration.

In addition, the individual must meet all of the following criteria:

• The individual actively participates in a comprehensive rehabilitation program that includes psychosocial support; AND
• The individual is not currently on opioid analgesics or physiologically dependent on opioids or currently in acute opioid withdrawal; AND
• The individual does not have a positive urine screen for opioids or a failed naloxone challenge test; AND
• The individual does not have acute hepatitis or liver failure.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
Alcohol Dependence
The efficacy of injectable Vivitrol® was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial. There were 624 alcohol dependent subjects who were randomized into three outpatient groups. Two groups received monthly injections. One group received Vivitrol® 190 mg (n=210) and the other group received Vivitrol® 380 mg (n=205). The third group (n=209) received a matching volume placebo. Both treatment and placebo groups received psychosocial intervention in addition. Compared with placebo, the group receiving Vivitrol® 380 mg demonstrated a statistically significant 25% reduction in the event rate of heavy drinking days while the group receiving 190 mg of Vivitrol® resulted in a 17% decrease. Gender and pretreatment abstinence each showed significant impact with the medication group on treatment outcome. Males and those who were alcohol abstinent for 7 consecutive days prior to treatment exhibited greater treatment effects. In contrast, the treatment effect was not evident in those who were actively drinking at the start of treatment (Garbutt, 2005).

Vivitrol® is marketed as providing increased compliance as compared to the oral formulation of naltrexone. However, there are no trials to substantiate the claim that increased compliance leads to better outcomes through either increased rates of abstinence or increased time to a first heavy drinking day. A heavy drinking day is defined as 5 or more standard drinks consumed on a given day for male patients and 4 or more standard drinks consumed on a given day for female patients. The monthly injection method of administration addresses non-compliance with the oral medication regimen and reduces first-pass hepatic metabolism as compared to oral naltrexone.
Alcoholism is divided into 2 categories: dependence and abuse. Alcohol dependence, the most severe alcohol disorder, is an interrelated cluster of psychological symptoms, such as craving; physiological signs, such as tolerance and withdrawal; and behavioral indicators, such as the use of alcohol to relieve withdrawal discomfort. Alcohol abuse implies intermittent alcohol use that causes either physical or mental impairment without dependence.

Nearly 14 million Americans meet diagnostic criteria for alcohol use disorders. For many of these individuals, oral medication and rehabilitation successfully treat their dependence. The oral medications work in different ways:

- naltrexone (Depade®, Revia®): acts within the brain to reduce craving for alcohol after alcohol intake has stopped;
- acamprosate (Campral®): is thought to work by reducing symptoms that follow lengthy abstinence, such as anxiety and insomnia;
- disulfiram (Antabuse®): discourages drinking by inducing a 'sick' feeling, much like a hangover, after alcohol intake; may have significant risks and side effects.

When an individual is on oral medication therapy, Depade® or Revia®, and fails to achieve and maintain alcohol abstinence, Vivitrol®, the injectable form of naltrexone, may be an option. Vivitrol® is injected monthly by a healthcare provider. The monthly injections are combined with ongoing rehabilitation.

Opioid dependence

The safety and efficacy of Vivitrol® were studied for six months, comparing Vivitrol® treatment to placebo treatment in patients who had completed detoxification and who were no longer physically dependent on opioids. Patients treated with Vivitrol® were more likely to stay in treatment and to refrain from using illicit drugs. The number of patients able to stay in treatment for the full 6 months without using drugs was 36% for the Vivitrol® treated group and 23% for the placebo treated group.

Patients must not have any opioids in their system when they start taking Vivitrol®; otherwise, they may experience withdrawal symptoms from the opioids. Also, patients may be more sensitive to opioids while taking Vivitrol® at the time their next scheduled dose is due. If they miss a dose or after treatment with Vivitrol® has ended, patients can accidentally overdose if they restart opioid use.

Comer et al (2006) reported on the safety and efficacy of a sustained-release depot formulation of naltrexone in treating opioid dependence. There were 60 heroin-dependent adults who participated in a randomized, double-blind, placebo-controlled, 8-week trial. Patients were randomized to receive placebo, 192mg, or 384mg of depot naltrexone. Doses were given at weeks 1 and 5. The results showed that retention in treatment was dose related, with 39% of patients in the placebo group, 60% of patients in the 192mg group, and 68% of the 384mg group remaining in treatment at the end of 2 months. The mean time to dropout was 27 days for the placebo group, 36 days for the 192mg group, and 48 days for the 384mg group. The adverse effects were minimal.
**Key Words:**
Antabuse® (Disulfiram)
Campral® (Acamprosate)
Depade®
Naltrexone
Revia®
Vivitrol®

**Approved by Governing Bodies:**
In April, 2006, the U.S. Food and Drug Administration (FDA) approved the extended release injectable formulation of naltrexone (Vivitrol®) for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting and as part of a comprehensive management program that includes psychosocial support.

On October 12, 2010, the U.S. Food and Drug Administration (FDA) approved Vivitrol® to treat and prevent relapse after patients with opioid dependence have undergone detoxification treatment.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.
Pre-certification requirements: Not applicable
Pre-determination requirements: Pre-determinations will be performed as a courtesy review at the request of the physician and/or subscriber.

**Coding:**
CPT Codes:

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<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tr>
<td>J2315</td>
<td>Injection, naltrexone, depot form, 1 mg</td>
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**References:**
2. Centers for Medicare and Medicaid Services. *National coverage determination: outpatient hospital services for treatment of alcoholism.* NCD #130.2:


Policy History:
Medical Policy Group, November 2010
Medical Policy Administration Committee, December, 2010
Available for comment December 10, 2010 through January 24, 2011

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review)in Blue Cross and Blue Shield’s administration of plans contracts.