Drug Use Research & Management Program
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Abbreviated New Drug Evaluation: Naltrexone Injection

Month/Year of Review: November 2013
Generic Name: Naltrexone
Dossier Received: Pending
PDL CLASS: Alcohol/Opioid Dependence Treatment

End date of literature search: August, 31, 2013
Brand Name (Manufacturer): Vivitrol® (Alkermes, Inc.)

FDA Approved Indications: Naltrexone injection 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 naltrexone. It is also indicated for the prevention of relapse to opioid dependence following opioid detoxification. It should be part of a comprehensive management program that includes psychosocial support.[1]

Research Questions:

- What is the evidence for the effectiveness of naltrexone injection in the treatment of alcohol and opioid dependence? What is the evidence for the safety of naltrexone injection for the treatment of alcohol and opioid dependence?
- Are there subpopulations that will benefit from naltrexone injection in terms of effectiveness or harms for the treatment of alcohol and opioid dependence?

Conclusions:

- For the treatment of alcohol dependence, there is moderate level of evidence that when compared to placebo, naltrexone extended-release injectable suspension reduces the rate of self-reported heavy drinking days and return to any drinking (RR 0.92, 95% CI 0.84-1.00).[2,3]
- For the treatment of opioid dependence, there is moderate level evidence that when compared to placebo, naltrexone extended-release injectable suspension is associated with reduced opioid use after detoxification and improves confirmed total abstinence in 35.7% vs. 22.6% (p = 0.0224, NNT 8) of patients when studied for 24 weeks, in combination with drug counseling.[4]
- There is moderate level of evidence that when compared to placebo, injectable naltrexone results in more discontinuations due to side effects (RR 1.57, 95% CI 0.92 to 2.69).[5]
- Extended release naltrexone is a viable option when medication adherence is a significant concern.

Recommendations

- Make nalgrexone extended release injection non-preferred AND
- Require prior authorization on its use due to insufficient efficacy and safety evidence comparing naltrexone extended-release injectable suspension to other currently available drug treatments for opioid dependence with the following criteria: (Appendix B)
    - The failure of other oral agents for the treatment of opioid dependency OR the patient requires injectable therapy
    - The member is part of a comprehensive treatment program for substance abuse that includes a psychosocial support system.

- Patients must be opioid free for 7 days prior to administration.
- Allow use of naltrexone injection in alcohol dependence until a subsequent full evidence review is completed.

Background/Current landscape

Naltrexone is a highly effective opioid antagonist that binds to mu-receptors. It has a higher affinity for mu receptors than has heroin, morphine, or methadone. It displaces those drugs from receptors and blocks their effects. As a result, it can precipitate withdrawal in patients who have not been abstinent from opioids.[6] Naltrexone displaces buprenorphine to a lesser degree, but when used in higher doses, it overrides buprenorphine's activity as well. The mechanisms responsible for the reduction in alcohol consumption are not entirely understood. Naltrexone has no narcotic effects, there are no withdrawal symptoms when discontinued, nor does naltrexone have abuse potential. The FDA approved naltrexone in tablet form for opioid maintenance treatment in 1984 based on its pharmacological effects without requiring evidence showing efficacy in the clinical trials. Despite its potential advantages, it has little impact on the treatment of opioid dependence in the United States due to poor patient compliance.[6] DynaMed concludes that oral naltrexone has insufficient evidence in the treatment of opioid dependence and a Cochrane review found no significant differences between oral naltrexone and placebo in preventing relapse in opioid addicts after detoxification.[7] Extended release naltrexone under trade name Vivitrol® was first approved in 2006 for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment. In 2010 it was approved for the prevention of relapse to opioid dependence following opioid detoxification. It is administered by intramuscular (IM) injection once per month. Naltrexone extended release injection must be administered by a healthcare professional and therefore it is currently covered under the medical benefit. There is limited head to head evidence evaluating extended-release naltrexone injection. A sustained release naltrexone implant has been shown to result in more patients with opioid dependency to remain in treatment without relapse than oral naltrexone (52.9% vs. 15.7%; p<0.001, NNT 3).[8] However, this is currently not approved in the US. There was a recent feasibility pilot study that investigated the using XR-NTX for the treatment previously opioid-dependent parolees and probationers (N = 61), results showed that those who completed treatment (N = 21) had significantly fewer opioid-positive urines (4% vs. 44%; p = 0.003) and were less likely to have been incarcerated than those who had not completed treatment (15% vs. 50%; p = 0.011).[9]

Clinical Efficacy and Safety

Alcohol Dependence

Systematic Reviews:

AHRQ Review:

AHRQ recently released a draft comparative effectiveness review in October 2013 on Pharmacotherapy in Adults with alcohol-use Disorder in Outpatient Settings.[10] The review included 130 studies. Most patients met criteria for alcohol dependence; mean ages were in the 40s. For acamprosate and naltrexone, numbers needed to treat (NNT) to prevent one person from returning to any drinking were 10 and 25, respectively (***Level of evidence: moderate***); NNT to prevent one person from returning to heavy drinking was 13 for naltrexone (***Level of evidence: moderate***). The meta-analyses of 3 head-to-head trials found no statistically significant difference between the two medications for consumption outcomes (***Level of evidence: moderate***). No RCTs assessing acamprosate or naltrexone were conducted in primary care settings. The authors found insufficient direct evidence to conclude whether medications for alcohol dependence are effective for improving health outcomes. Evidence was insufficient to determine comparative effectiveness of medications for subgroups.

Compared with placebo, patients treated with acamprosate had a higher risk of anxiety, diarrhea, and vomiting; those treated with naltrexone had a higher risk of dizziness, nausea, and vomiting. In head-to-head studies, the risk of headache was higher for naltrexone than for acamprosate.
The authors concluded acamprosate and naltrexone had the best evidence of efficacy for improving alcohol consumption outcomes for patients with alcohol dependence. Head-to-head trials have not consistently established superiority of one medication. Other factors, such as frequency of administration, potential adverse events, coexisting symptoms, and availability of treatments should be taken into consideration of medication choices.

Cochrane Review:

A 2010 systematic review from the Cochrane Collaboration evaluated the effectiveness and tolerability of opioid antagonists in the treatment of alcohol dependence.[5] All double-blind RCTs comparing naltrexone or nalmefene with placebo or active control were included. Primary outcomes included: return to heavy drinking, return to any drinking, and drinking days. A literature search through January 2010 identified 50 studies (n=7,793) to be included in the evidence synthesis; 47 of which were included in the meta-analysis. Only 4 of the RCTs evaluated the injectable ER formulation of naltrexone. These trials showed that injectable naltrexone appears effective, but not all outcomes were statistically significant. Injectable naltrexone was administered at four-week intervals at doses between 150 mg and 400 mg.

Analysis of injectable naltrexone showed reduced risk of any drinking after detoxification to 92% of the placebo group (RR 0.92, 95% CI 0.84-1.0), the percentage of drinking days by about 9% (mean difference [MD] -8.54, 95% CI -15.77 to -1.31), and the percentage of heavy drinking days by about 3% (MD -3.05, 95% CI -8.46 o 2.35). Injectable naltrexone caused significantly more daytime sleepiness, decreased appetite, dizziness, fatigue, and vomiting than placebo. Early withdrawals due to side effects were more frequent in the injectable naltrexone group than the placebo group (RR 1.57, 95% CI 0.92 to 2.69).

Authors concluded that the treatment effects of injectable naltrexone are comparable in magnitude to oral naltrexone. However, statistical significance was missed. Other than a more pronounced sedative effect, the tolerability appears comparable to oral naltrexone.

Clinical Trials:

Naltrexone extended-release injectable suspension was assessed in a 24-week placebo-controlled, multicenter, double-blind, randomized study enrolling 624 outpatients meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for alcohol dependence.[2] Injections of placebo (209 patients), naltrexone 190 mg extended-release (210 patients), or naltrexone 380 mg extended-release (205 patients) were administered IM every 4 weeks. Oral naltrexone was not administered prior to the initial or subsequent injections. Low-intensity psychosocial support was provided to all subjects. A total of 6 injections were administered to 401 patients (64%), while 463 patients (74%) received 4 injections. The primary study end point was the reduction of rate of heavy drinking days in the intent-to-treat population. Patients treated with naltrexone 380 mg extended-release injection had a greater reduction in days of heavy drinking (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) compared with those treated with placebo. Heavy drinking days were reduced 25% in the naltrexone 380 mg group (P = 0.03) and 17% in the naltrexone 190 mg group (P = 0.07) compared with placebo. Greater reductions in heavy drinking days were observed in those abstinent at study entry and in men. During the study, complete abstinence was maintained in 7% of patients in the 380 mg group, 6% in the 190 mg group, and 5% in the placebo group. The results suggested even though there was clinically significant reduction in self reported heavy drinking days in treatment groups, it did not result statistically significant difference in abstinence between groups, which is the optimal treatment goal. The subgroup analysis on 53 patients who abstained completely from drinking during the week prior to the first dose of medication and were treated with naltrexone 380 mg extended-release injection had greater reductions in the number of drinking days and the number of heavy drinking days compared with those treated with placebo. In this subgroup, patients treated with naltrexone were also more likely

than placebo-treated patients to maintain complete abstinence throughout treatment (41% vs. 35% in the 190 mg group and 17% in the placebo group; differences not statistically significant).[2]
Naltrexone extended-release injectable suspension was also assessed in a 3-month randomized, double-blind, placebo-controlled study enrolling 315 alcohol-dependent subjects.[3] Patients received naltrexone (158 patients) or placebo (157 patients) monthly for 3 months. The primary endpoint was cumulative number of heavy-drinking days, during the treatment period. The naltrexone dose was 300 mg (two 150 mg injections) for the first dose and 150 mg for the subsequent doses. All patients also received 5 sessions of manual-guided motivational enhancement therapy. The time to first drinking day, percentage of patients with no heavy drinking throughout the study, and gamma-glutamyl transpeptidase levels all favored the naltrexone, but were not statistically significant. The median time to first heavy drinking day was 11 days in the naltrexone group compared with 6 days in the placebo group (*P* = 0.05). The mean number of heavy drinking days was 22.4 in the naltrexone group compared with 25.3 in the placebo group (*P* = 0.29). The median time to first drinking day was 5 days in the naltrexone group compared with 3 days in the placebo group (*P* = 0.003). During the 12-week study, 23% of the naltrexone depot group reported no heavy drinking, compared with 16% of placebo (p = 0.12)[3]

The commonly reported adverse reactions during clinical trials for the treatment of alcohol dependence with naltrexone 380 mg extended-release injectable suspension compared with placebo included nausea (33% vs. 11%), vomiting (14% vs. 6%), diarrhea (13% vs. 10%), abdominal pain (11% vs. 8%), injection-site reactions (69% vs. 50%; tenderness, induration, pain, swelling), asthenia (23% vs. 12%), headache (25% vs. 18%), dizziness (13% vs. 4%), and decreased appetite (14% vs. 3%). The most common adverse reactions prompting discontinuation of therapy were injection-site reactions (3%), nausea (2%), pregnancy (1%), headache (1%), and suicide-related events (0.3%). Nausea is most common after the first injection. It is generally mild and subsides within a few days post injection. Nausea is less likely to occur following subsequent injections.[1]

Opioid Dependence

Systematic Reviews:
A Cochrane systematic review of sustained-release depot naltrexone for opioid dependence published in 2008 concluded that evidence was insufficient to evaluate its effectiveness.[11] However, this was before the following clinical trials were completed and was evaluating a slightly different formulation.

Clinical Trials:
The efficacy of naltrexone extended-release injectable suspension 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.[4] A total of 250 eligible patients were randomized to receive naltrexone 380 mg (n = 126) or placebo (n = 124), both in combination with drug counseling. The primary endpoint was confirmed abstinence, calculated by each patient's rate of opioid-free weeks. All missing urine drug test results were imputed as positive for opioid use. Results demonstrated opioid-free weeks from week 5 to 24 weeks were significantly different between treatment groups (P = 0.0002), with a median of 90% opioid-free urines in the extended-release naltrexone group and 35% in the placebo group. In addition, significantly more naltrexone -treated patients achieved complete abstinence from Week 5 to Week 24 vs. placebo-treated patients (36% vs. 23%, respectively; P = 0.0224).[4] Overall, 51% of the naltrexone -treated patients and 65% of the placebo-treated patients did not complete the 24 weeks of treatment and 13% of naltrexone-treated patients compared to 36% of placebo-treated patients dropped out of the study before week 5.

Patients who completed this initial 6-month study were offered to enroll in a 1-year open-label extension study which provided injectable naltrexone for up to 13 additional doses.[12] Overall, 50.9% of patients remained abstinent from opioids at all scheduled monthly assessments during the open-label phase (49.3% of those continuing with naltrexone vs. 53.2% of those who switched from placebo).
There was another multicenter, randomized, double-blind, placebo-controlled, parallel, 8 –week clinical trial that evaluated the safety and efficacy of long acting injectable naltrexone (Depotrex®) in the treatment of opioid dependence.[13] However, this formulation is not available in the US. It is not included in the review.

In the clinical trial of opioid-dependent patients, 2% of patients treated with injectable naltrexone and 2% of patients treated with placebo discontinued treatment due to an adverse event (AE).[1] The treatment-emergent AEs, regardless of causality, occurring in ≥ 2% of patients for which the incidence was greater in the injectable naltrexone group vs. placebo, were: alanine aminotransferase (ALT) increased (13%), aspartate aminotransferase (AST) increased (10%), gamma-glutamyltransferase (GGT) increased (7%), nasopharyngitis (7%), influenza (5%), insomnia (6%), hypertension (5%), injection site pain (5%), toothache (4%), and headache (3%).[1]

Evidence Table:

Relevant Endpoints:

1) Return to drinking
2) Complete abstinence
3) Discontinuations due to Adverse events

Study Endpoints:

1) Confirmed abstinence or self-reported drinking days
2) Opioid craving score, percent of drinking/no drinking days
3) Relapses
4) Discontinuation rate

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH	Quality Rating[4]; Comments
Garbutt J[2] et al.– alcohol dependence 2005 DB, PC, RCT; MC	N1: 380mg naltrexone N2: 190 mg naltrexone P: placebo	Mean age (N1/N2/P): 45.0/44.6/44.7 Male (N1/N2/P): 67%/68%/66% Caucasian (N1/N2/P): 83.9%/80.5%86.1% % Heavy drinking in 30 days before randomization (N1/N2/P): 25.9/26.4/24.8 Inclusion criteria: ≥18 years of age, had minimum of 2 episodes of heavy drinking per week during 30 days before screening. Exclusion criteria: Evidence o liver failure; ALT or AST > 3x normal limits; dependence within the past year on benzodiazepines, opiates, or cocaine; > 7 days of inpatient tx for substance abuse in the month before screening.	N1: 205 N2: 210 P: 209	24 weeks	Primary endpoint Reduction of Rate of heavy drinking days compared to placebo: N1: 25% (p = 0.03) N2: 17% (p = 0.07) Secondary endpoint Drinking risk reductior compared to placebo: N1: 10% (p = 0.23; NS) N2: 5% (p = 0.58; NS) Reduction of non abstinent days compared to placebo: N1: 4% (p = 0.58; NS) N2: 2% (p = 0.80; NS)	N1: ARR25% NNT 4 N2: ARR17% NNT 6 NA NA	Tx related events (N1/N2/P) N1:5.4% N2:4.8% P:7.2% p value not reported Discontinuation due t AE:: N1:29 (14.1%) N2: 14 (6.7%) P; 14 (6.7%) p = 0.01, N1 vs. N2 an P)	NA ARR 7.4% NNH 13.5	Fair Internal Validity Review of Bias: Selection: Low bias; the randomization and allocation concealment was clear. Performance: Low bias; blinding of patients and study monitors Attrition: High attrition at 39.5%, 40% and 38.9% for naltrexone 380mg, 190mg and placebo respectively. ITT analysis. External Validity Review of Bias: Patient characteristics: Majority pts were Caucasian in range of 80.5 -86.1% among groups. Male consisted 2/3 of the all study groups and differed characteristics from female participant such as concurrent drug use, baseline LFTs. Setting: The study included patients from both public and private treatment settings, and specialty and non-specialty practices. Outcomes: The primary efficacy was based on pt's self report. Although pt was subject to breath alcohol levels, but it is unclear the frequency of the test and who was conducting the test. In addition, it was a short term study investigating potential long term addiction with multiple relapses. Because the study included wide range of patients in different setting, it is unclear which subgroup would potentially benefit the most from the treatment.

Kranzler[3] et. al **– alcohol dependence** 2004 DB, PC, RCT; MC	ND: naltrexone depot 150mg monthly with 300mg loading dose P: placebo	Mean age (ND/P): 44.1/43.6 Female (ND/P): 32.9%/36.9% Caucasian (ND/P): 82.9%/81.5% Alcohol dependence scale, mean (SD): ND: 19.3 (7.7)* P: 17.5 (7.2)* *p < 0.05 Pretreatment heavy-drinking days in 30 days, mean (SD): ND: 20.3 (7.8) P: 21.5 (7.0)	ND = 158 P = 157	12 weeks	Primary endpoint Cumulative #of heavy-drinking days during the treatment period, mean (95% CI): ND: 22.4 (18.3 -26.4) P: 25.3 (21.3 – 29.4) P value = 0.29 (NS) Selected Secondary endpoint Cumulative abstinent days, mean (95% CI) during study period: ND: 52.8 (48.5 – 57.2) P: 45.6 (41.1 – 50.0) P value = 0.018 Time to 1st heavy drinking day, median (95% CI): ND: 11 (8-17) P: 6 (4-10) P Value = 0.05 (NS)	NA NA N/A	Discontinuations due to AE ND: 4 (2.5%) P: 2 (1.3) p-values not provided	NA	Fair Internal Validity Review of Bias: Selection: Low bias; the randomization and allocation concealment was clear. Performance: Potential bias; blinding of patients was described; however it was unclear the binding of the study monitors Attrition: Attrition rates for treatmen and placebo groups at 19.6% and 28.7% respectively, which were lower than other RCT. ITT analysis. External Validity Review of Bias: Patient characteristics: Majority pts were Caucasian and female pts. The concurrent use of other medications was unknown. Participants were subjects who responded to media advertisement or referred by community clinicians who were treatment-seeking individuals, which potentially limit generalizability. Setting: The study was conducted in 30 treatment centers. Pts were provided with 5 sessions of motivational enhancement therapy (MET). Outcomes: The primary efficacy was based on pt's self report. No secondary method to ensure the accuracy of the self-reporting results. The primary goal of abstinence can't be fully demonstrated in a short term study. The study was not a direct comparison to oral naltrexone.

Krupitsky[4] et. al – opioid dependence, 2011 DB, PC, RCT; MC	ND: naltrexone extended release 380mg monthly P: placebo	Mean age (ND/P): 29.4/29.7 Male (ND/P): 90%/86% Caucasian (ND/P): 98%/100% Duration of opioid dependence (yrs) (ND/P): 9.1/10.0 Opioid craving scale (ND/P): 18/22	N: 250 ND: 126 P: 124	24 weeks	**Primary endpoints** Confirmed abstinence during week 5-24: 1. Proportion of wks of confirmed abstinence : ND: 90% P: 35% p =0.0002 2. % of pts with total confirmed abstinence: ND: 45 (35.7%) P: 25 (22.8%) RR 1.58, 95% CI1.06 – 2.36); p = 0.0224 **Secondary endpoints** Proportion of self-reported opioid-free days over 24 wks:: ND: 99.2% P:60.4% p = 0.004	N/A ARR12.9% NNT 8 ARR 38.8% NNT3	Discontinuation due to AE: ND: 2 (1.6%) P: 2 (1.6%)	**NS**	Fair Internal Validity Review of Bias: Selection: Low bias; the randomization and allocation concealment was clear. Performance: Low bias; blinding of patients and study monitors Attrition: High attrition at 46.8% and 62.1% for treatment group and placebo group respective. ITT analysis. External Validity Review of Bias: Patient characteristics: predominantly young white males. Setting: The study was conducted in Russia where opioid agonist therapy i unavailable. The high retention rate i placebo group may influenced by lack of accessibility to opioid agonist. Generalizability of its use in the U.S needs further research. Outcomes: The primary goal of abstinence can't be fully demonstrated in a short term study. The study was not a direct comparison to oral naltrexone.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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Appendix A: Specific Drug Information

CLINICAL PHARMACOLOGY[1]

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. Naltrexone inj. ® is an extended-release, microsphere formulation of naltrexone designed to be administered by intramuscular (IM) gluteal injection every 4 weeks or once a month.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): Naltrexone is contraindicated in patients receiving opioid analgesics; patients with current physiologic opioid dependence; patients in acute opioid withdrawal; any individual who has failed the naloxone challenge test or has a positive urine screen for opioids; or patients who have previously exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluents.

Tolerability: Serious adverse reactions that may be associated with naltrexone injection 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 naltrexone injection therapy for alcohol dependence (ie, those occurring in ≥ 5% and at least twice as frequently with naltrexone injection 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 naltrexone injection therapy in opioid dependent patients (ie, those occurring in ≥ 2% and at least twice as frequently with NALTREXONE INJ. than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

Pregnancy/Lactation rating: C. There are no adequate and well-controlled studies of naltrexone injection in pregnant women. naltrexone injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Reproduction and developmental studies have not been conducted for naltrexone injection. Studies with naltrexone administered via the oral route have been conducted in pregnant rats and rabbits

Look-alike / Sound-alike (LA/SA) Error Risk Potential

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for perampanel [generic]	None	None	None	None	Nalfon®, naloxone, nalbuphine
LA/SA for Fycompa™[brand]	None	None	None	None	Vivactil®, Vivarin®, Vivotif®

ADVERSE REACTIONS[1]

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	%
Disorders	Vomiting NOS	12	6	3	12	28	14	22	10	53	12
	Diarrhea[a)]	21	10	3	12	27	13	27	13	57	13
	Abdominal pain[b)]	17	8	4	16	23	11	23	11	50	11
	Dry Mouth	9	4	6	24	10	5	8	4	24	5
Infections & Infestations	Pharyngitis[c)]	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
	Anxiety[d)]	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 conditions[e)]	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 cramps[f)]	3	1	0	0	16	8	5	2	21	5
Skin & Subcutaneous Tissue Disorders	Rash[g)]	8	4	3	12	12	6	10	5	25	6
Nervous System Disorders	Headache[h)]	39	18	9	36	51	25	34	16	94	21

Table 2: Treatment-emergent Clinical Adverse Events (Events in ≥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

DOSE & AVAILABILITY:[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
380mg	Injection	IM	Every 4 weeks or once a month	Mild impairment; no adjustment; moderate to severe impairment: not defined, caution advised.	Mild impairment; no adjustment; moderate to severe impairment: not defined, caution advised. Acute hepatitis/hepatic failure: contraindicated	NA	Same as adult dose.	Must be opioid free for 7-10 days; consider naltrexone challenge test if risk of withdrawal suspected. Must be administered by healthcare professional.

PHARMACOKINETICS:[1]

Parameter	Result
Oral Bioavailability	NA
Tmax	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.
Protein Binding	Approximately 21%
Elimination	Primarily via urine, with minimal excretion of unchanged naltrexone.
Half-Life	About 5-10 days.
Metabolism	The cytochrome P450 system is not involved in naltrexone metabolism. Production of the primary metabolite, 6β-naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes.

ALLERGIES/INTERACTIONS:[1]

Drug-Drug: Because naltrexone is not a substrate for CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes are unlikely to change the clearance of Naltrexone inj. ®. 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. Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations, and opioid analgesics.

Appendix B: Suggested PA Criteria

Naltrexone Extended Release Inj. (Vivitrol)

Goal(s):

- Promote safe and cost effective therapy for the treatment of alcohol and opioid dependence.

Length of Authorization: Initial – 3 months; Renewal – one year

Covered Alternatives: Acamprosate, naltrexone tablets, disulfiram

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the member have a diagnosis of alcohol dependence?	**Yes:** Go to #3.	**No:** Go to #4
3. Has the requesting prescriber provided documentation and/or confirmation of abstinence from alcohol as assessed by the provider and/or objective testing?	**Yes:** Go to #6	**No:** Deny, medical appropriateness. Patients must have demonstrated alcohol abstinence prior to administration.
4. Does the member have a diagnosis of opioid dependence?	**Yes:** Go to #5	**No:** Deny, medical appropriateness. Naltrexone extended release injection is only approved for alcohol and opioid dependence.
5. Has the patient tried and failed other oral agents for the treatment of opioid dependency (buprenorphine, methadone) OR Does the patient require injectable therapy?	**Yes:** Go to #6	**No:** Deny, medical appropriateness.
6. Is the member part of a comprehensive treatment program for substance abuse that includes a psychosocial support system?	**Yes:** Go to #7	**No:** Deny, medical appropriateness. Naltrexone extended release injection therapy must be part of a comprehensive treatment program including psychosocial support.

Approval Criteria		
7. Has the patient received any opioid prescription within the last 30 days from a prescriber other than the requesting provider based on prescription claims history?	**Yes:** Notify requesting provider of the opioid prescriber, drug, dose, prescription date and the day supply; Go to #8.	**No:** Go to #8
8. Has the patient abstained from the use of any opioids for at least 7 to 10 days, including street opioids such as heroin or prescription opioids as assessed by the provider and/or objective testing?	**Yes:** Approve for 3 months for initial therapy, 12 months for continuation therapy	**No:** Deny, medical appropriateness. Patient must be opioid free for 7 to 10 days prior to administration to minimize risk of acute opioid withdrawal syndrome.

P&T Action: *11/21/2013 (TW/MH)*
Revision(s):
Initiated: