



Technology Assessment Report

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Name of the Technology and DSM-IV Disorder of Focus:

VIVITROL™ (naltrexone for extended-release injectable suspension) for the treatment of Opiate Addiction

Description of the Technology:

VIVITROL™ is supplied as a microsphere formulation of naltrexone for suspension, to be administered by intramuscular injection. This version is made by *Alkermes*, and is jointly marketed by *Cephalon, Inc.*. Naltrexone is an opioid antagonist with highest affinity for the μ opioid receptor and has few, if any intrinsic actions besides its opioid blocking properties. The administration of VIVITROL is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, VIVITROL will precipitate withdrawal symptomatology.

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, involvement of the endogenous opioid system is suggested by preclinical data.

Naltrexone blocks the effects of opioids by competitive binding at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of opioids may result in non-opioid receptor-mediated histamine release. VIVITROL is not aversive therapy and does not cause a disulfiram-like reaction as a result of opiate or alcohol ingestion. VIVITROL does not eliminate or diminish alcohol withdrawal.

The once monthly injection must be administered by a healthcare professional and is intended for use in combination with psychosocial support, such as counseling or group therapy. The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks. Pretreatment with oral naltrexone is not required prior to use of the injection.

1. Technology must have final approval from the appropriate government regulatory bodies.

Depot injectable naltrexone **VIVITROL™** was approved by The Food and Drug Administration (FDA) on April 13, 2006 for the treatment of alcohol dependence in patients who are able to abstain from drinking in an outpatient setting and who are not actively drinking at therapy

initiation. (Note: The FDA approved the 50 mg. oral tablet form of naltrexone hydrochloride on November 20, 1984 for the treatment of Opioid Dependence. In 1994, the FDA approved oral naltrexone tablets as an adjunct to therapy for alcoholism).

The FDA approval for **VIVITROL™** specifically notes that use of this product is contraindicated in the following situations:

- patients receiving opioid analgesics
- patients who have current physiologic opioid dependence or a positive urine screen for opioids
- patients in acute opiate withdrawal

Patients must be opioid free for a minimum of 7 to 10 days prior to initiation of therapy to prevent symptoms of opioid withdrawal or exacerbation of a preexisting subclinical abstinence syndrome. The FDA warns that attempts to overcome naltrexone-induced opioid blockade by using exogenous opioids may result in fatal overdose, particularly in patients with a previous history of opioid abuse. If naltrexone reversal is indicated for pain management, patients should be monitored in a setting equipped and staffed for cardiopulmonary resuscitation.

2. The scientific evidence must permit conclusions about the effects of the technology on health outcomes. (Conclusive evidence in peer-reviewed medical literature to enable the evaluation of the effectiveness and efficacy of the procedure or drug.)

Levels of Evidence are defined as follows:

Level 1: Randomized trials that had enough power to demonstrate a statistically significant health outcome.

Level 2: Randomized trials with results that were not statistically significant but where a larger trial might have shown a clinically important difference.

Level 3: Nonrandomized concurrent cohort comparisons between contemporaneous patients.

Level 4: Nonrandomized historical cohort comparisons between current patients and former patients (from the same institution or from the literature).

Level 5: Case series without control subjects.

Treatment of Alcohol Dependence:

Manufacturer (Alkermes) Clinical Development Study 2003 – (Level 1)

The efficacy of VIVITROL in the treatment of alcohol dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of alcohol dependent (DSM-IV criteria) outpatients. Subjects were treated with an injection every 4 weeks of VIVITROL 190 mg, VIVITROL 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Psychosocial support was provided to all subjects in addition to medication.

Subjects treated with VIVITROL 380 mg demonstrated a greater reduction in days of heavy drinking than those treated with placebo. Heavy drinking was 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. Among the subset of patients (n=53, 8% of the total study population) who abstained completely from drinking during the week prior to the first dose of medication, compared with placebo-treated patients, those treated with VIVITROL 380 mg had greater reductions in the number of drinking days and the number of heavy drinking days. In this subset, patients treated with VIVITROL were also more likely than placebo-treated patients to maintain complete abstinence throughout treatment. The same treatment effects were not

evident among the subset of patients (n=571, 92% of the total study population) who were actively drinking at the time of treatment initiation.

Treatment of Opioid Dependence:

Phase II (Alkermes sponsored) Exploratory Study (Johns Hopkins and National Institute on Drug Abuse - NIDA) 2006 – (Level 1)

The Phase II double-blind, “off-label usage” exploratory study was designed by the manufacturer of VIVITROL to assess the efficacy and tolerability of injectable extended-released naltrexone (XR-NTX) in 27 opioid-using adults who had used opioids non-medically for at least one year and were physically dependent on opioids. Subjects were randomized to receive a single intramuscular administration of extended-release naltrexone at one of three doses (75mg, 150 mg, or 300 mg). At repeated intervals throughout the 8 week study, the level of opioid blockade by XR-NTX was assessed by administering increasing doses of the opioid hydromorphone at one hour intervals, with a maximum cumulative dose of 13.5 mg. Measures of efficacy included a subjective response to a self-rated visual analog scale (VAS) question “Do you feel any drug effect?” and pupil size measurement following a dose of hydromorphone 3 mg. Investigators also assessed subjects for drug intoxication following increasing doses of hydromorphone.

Study Results: In the study, subjective responses based on the VAS question indicated that blockade of hydromorphone 3 mg. was achieved for at least 28 days with XR-NTX 150 mg and XR-NTX 300mg, and for at least 21 days with XR-NTX 75 mg. Subjective responses of the blockade of opioid effects reported by patients are considered the most relevant measure in this study from a therapeutic perspective. Pupil size measurements confirmed the substantial and extended-duration blockade of hydromorphone 3 mg by XR-NTX. Based on investigator assessment of drug intoxication, at day 28, 83% of subjects who received XR-NTX 300 mg were able to receive the maximum cumulative dose of 13.5 hydromorphone without excessive intoxication; dose dependent blockade was also evident for XR-NTX 150 mg and 75 mg.

Injectable extended-released naltrexone was generally tolerated. No serious or severe adverse events occurred during the study. The most commonly reported adverse events were headache and fatigue, and the incidence of adverse events were similar for all three dose groups.

Other Depot Naltrexone Drugs Under Study:

- **Depotrex®** (depot Naltrexone microcapsules) – manufactured by *Biotek* of Woburn, MA. Currently conducting a Phase II study on its use in the treatment of opiate/alcohol dependence.
- **Naltrel®** (naltrexone depot for injection) – manufactured by *DrugAbuse* Pharmaceutical of Lexington, MA. Currently conducting Phase II studies on its use in the treatment of alcohol dependence and also for heroin dependence, opiate dependence.

3. *The technology is as beneficial (safe and effective) as existing alternative treatments.*

There are no published studies which compare VIVITROL to the established alternatives of oral naltrexone (opioid antagonist), methadone or LAAM (opioid agonists) and buprenorphine (partial μ opioid agonist) – the drugs currently approved by the FDA for opioid dependence and in use today.

4. *The technology improves the net health outcome, i.e., there is conclusive evidence that the benefits outweigh the risks.*

There is no conclusive evidence to date that VIVITROL improves net health outcome in the treatment of opioid dependence. Currently, there are no empirical data published from well-designed and controlled studies that can determine whether benefits outweigh the risks.

5. *The improvement in health outcomes is reliably obtainable outside investigational settings.*

Improvement in health outcomes resulting from use of VIVITROL for opioid dependence have not yet been established in an investigational setting and therefore cannot be determined to be useful outside of such a setting.

Conclusion (is the new technology proven or experimental, and summary of why):

The Technology Assessment Committee will review this technology again when further studies on the efficacy of VIVITROL in the treatment of opioid dependence have been conducted. At this time, VIVITROL, as a treatment for opioid dependence, is an investigational drug under development and has not been approved for this indication.

Determination: **Investigational**

Effective Date: March 5, 2007

REFERENCES:

1. VIVITROL. FDA Application No. (NDA) 021897 Approval History, Letter, Reviews and Related Documents, April 12, 2006.
2. FDA Approvals: Vivitrol CME/CE. Medscape Medical News. Accessed website on 12/22/07 www.medscape.com/viewarticle/530353_print.
3. Alkermes Announces Positive Data from Exploratory Study of Extended-Release Naltrexone for Blockade of Opioid Effect, *Alkermes*, Press Release, Cambridge, MA, December 4, 2006.