1ST Cycle

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS
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DIVISION DIRECTOR APPROVABLE MEMO

DATE:	December 23, 2005
DRUG:	Vivitrol™ (naltrexone for extended-release injectable suspension) Kit
NDA:	21-897
NDA Code:	Type 4P NDA
SPONSOR:	Alkermes, Inc.
INDICATION:	For the treatment of alcohol dependence

Alkermes, Inc. submitted NDA 21-897 in support of marketing approval for the Vivitrol™ (naltrexone for extended-release injectable suspension) Kit* on March 31, 2005. Vivitrol™ is a microsphere-based formulation comprised of naltrexone incorporated into a biodegradable matrix of polylactide-co-glycolide which is then suspended in an aqueous diluent and injected intramuscularly. The Division determined that the application merited a priority review due to purported claims of increased efficacy and safety compared to the available approved products to treat alcohol dependence. A major amendment was submitted towards the end of the review period, thus extending this period by three months.

The μ-opiate antagonist naltrexone was originally approved in 1984 "for the blockade of effects of exogenously-administered opioid," and subsequently for "the treatment of

* Includes: Vivitrol™ microspheres (one 380-mg vial), diluent (4-mL vial containing carboxymethycellulose sodium salt, polysorbate 20, sodium chloride, and sterile water for injection), needles (one 20 gauge ½ inch and two 20 gauge 1 ½ inch), one 5-mL prepackaged syringe, Patient Package Insert and Package Insert.

alcohol dependence" as part of an appropriate plan of management for addictions. Naltrexone has not been widely used for this indication due to the general belief that its efficacy is limited, and that poor compliance is one of the more significant factors contributing to this limited efficacy. The sponsor has proposed that an extended-release depot preparation may improve compliance and, therefore, effectiveness. They have also proposed that the absence of a first-pass effect in the liver may decrease the hepatic toxicity noted in the original naltrexone application resulting in the inclusion of a boxed warning in the package insert.

Review of the CMC portion of this application was completed by Jila H. Boal, Ph.D. Review of the pharmacology and toxicology data presented in this application was completed by Mamata De, Ph.D. A supervisory review was provided by Daniel Mellon, Ph.D., Supervisory Pharmacologist in this division. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by Srikanth C. Nallani, Ph.D. A clinical review of the safety and efficacy data submitted was completed by Mwango Kashoki, M.D., M.P.H. A statistical review and evaluation was completed by Dionne Price, Ph.D. Celia Winchell, M.D. provided a supervisory review of the application. Consultation on this application was also obtained from the Division of Pulmonary and Allergy Products (DPAP), the Division of Drug Marketing, Advertising and Communications (DDMAC), and the Office of Drug Safety (ODS).

As the clinical and statistical reviews have thoroughly detailed and analyzed the data submitted in this application, I will only briefly summarize their findings in this memo.

Efficacy:

A single adequate and well-controlled study was submitted in support of efficacy. **Study 21-003** (003) was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study comparing Vivitrol™ (190 mg or 380 mg) and placebo for six months. Adults meeting the DSM IV diagnostic criteria for alcohol dependence, and who had at least two episodes of heavy drinking (4 drinks per day for women and 5 drinks per day for men) per week were admitted to the study. Complete abstinence at baseline was not required. Subjects received monthly intramuscular injection of drug or placebo in the gluteal muscle.

Alcohol consumption was collected using the Time Line Follow-back Method and the quantity then converted into a number of standard drinks using a protocol-specified definition/formula. Psychosocial treatment was provided using the BRENDA (Biopsychosocial, Report, Empathy, Needs, Direct advice and Assessment of responsiveness) model. The protocol-specified primary outcome analysis was a comparison of the event rate of heavy drinking with heavy drinking defined as at least four drinks per day for women and five drinks a day for men.

Recent analyses conducted by the NIAAA documented an apparent link between various patterns of drinking and the likelihood of drinking-related psychosocial consequences. The results of these analyses suggest that the strongest predictor of avoiding significant consequences is the absence of any heavy drinking days (employing observation periods of 3 to 12 months), with heavy drinking days defined as more than four drinks for males and more than three drinks for females. Therefore, at the request of the Division, a responder analysis was performed to add perspective on the clinical relevance of the results of the primary analysis. The agreed upon responder categories included:

- no heavy drinking days per month
- 0 and $\leq$ 1 heavy drinking day per month
- 1 and $\leq$ 2 heavy drinking days per month
- 2 and $\leq$ 3 heavy drinking days per month
- 3 and $\leq$ 4 heavy drinking days per month
- 4 heavy drinking days per month

The results of the primary outcome analysis demonstrated a statistically significant treatment effect for the 380-mg dose only. Dr. Price's Table 5 summarizing this data is reproduced below:

Comparison of Median Event rate of Heavy Drinking: Non-Parametric Analyses
Any missing data day is defined as a heavy drinking day

Treatment Group	N	Median Event Rate of Heavy Drinking	Percent Difference	p-value* Wilcoxon test unstratified
Placebo	204	0.35		
190 mg	206	0.30	13%	0.69
380 mg	201	0.20	41%	0.05

*p-value compared to placebo

The sponsor also analyzed the data based on abstinence at baseline (defined as abstinent for 7 days prior to treatment) and based on subjects' treatment goal at baseline (total abstinence or several other options). While the subjects' treatment goal did not appear to influence the outcome, whether or not a subject was abstinent at baseline had a profound effect on the subject's response to treatment. The data supporting this conclusion is summarized in Dr. Winchell's table from page 12 of her review, reproduced below:

FACTOR		NUMBER OF SUBJECTS PLACEBO	190 MG	380 MG	HAZARD RATIO (P-VALUE) 190 MG VS. PLACEBO	380 MG VS. PLACEBO
Lead-in Drinking	Yes	190	193	188	0.925 (0.4803)	0.790 (0.0532)
	No	19	17	17	0.049 (<0.0001)	0.202 (0.0053)
Treatment Goal of Abstinence	Yes	90	90	90	0.879 (0.4994)	0.718 (0.1119)
	No	119	120	115	0.912 (0.4841)	0.785 (0.0991)

The results of the responder analysis showed a small effect of treatment and only at greater than 1 heavy drinking day per month. However, when the effect of abstinence at baseline was included in the analysis, a much larger effect was seen for all strata, including 0 heavy drinking days per month. The data supporting these conclusions are summarized in Dr. Winchell's tables from pages 13 and 14 of her review, reproduced below:

Responder analysis using 5/4 definition of responders and 2-month grace period.

HDD per month	Placebo (n=204)	190 mg (n=206)	380 mg (n=201)
0	22 (11%)	25 (12%)	26 (13%)
0-1	36 (18%)	37 (18%)	39 (19%)
0-2	47 (23%)	51 (25%)	61 (30%)
0-3	52 (26%)	59 (29%)	70 (35%)
0-4	56 (28%)	65 (32%)	79 (39%)

Responder analysis using 5/4 definition of responders and 2-month grace period.

	Placebo		190 mg		380 mg	
HDD per month	Non-abstinent (n = 186)	Abstinent (n=18)	Non-abstinent (n = 189)	Abstinent (n=17)	Non-abstinent (n = 184)	Abstinent (n=17)
0	20 (11%)	2 (11%)	15 (8%)	10 (59%)	19 (10%)	7 (41%)
0-1	31 (17%)	5 (28%)	27 (14%)	10 (59%)	30 (16%)	9 (53%)
0-2	40 (22%)	7 (39%)	41 (22%)	10 (59%)	49 (27%)	12 (71%)
0-3	44 (24%)	8 (44%)	49 (26%)	10 (59%)	58 (32%)	12 (71%)
0-4	48 (26%)	8 (44%)	55 (29%)	10 (59%)	65 (35%)	14 (82%)

Clinical Safety:

Exposure

Over one thousand subjects were exposed to Vivitrol™. Dr. Winchell's summary table of exposure by number of injections (page 16 of her review) is reproduced below:

	<380 mg	≥380 mg
At least 1 injection	349	700
At least 3 injections	217	541
At least 6 injections	177	394
At least 12 injections	98	127
At least 18 injections	56	59
At least 24 injections	27	22

Deaths

Five deaths occurred in the Vivitrol™ database. Based on Drs. Kashoki and Winchell's reviews, only two of those deaths were possibly related to study drug exposure. These two deaths were both suicides in subjects treated with study drug for extended periods of time. One occurred after five months of treatment, but not until two months after the last dose. The other occurred after the subject had received 33 doses.

Discontinuations Due to Adverse Events (AEs)

There was a slightly higher rate of dropout due to adverse events for the study drug-treated subjects compared to the placebo-treated subjects. However, there was no clear dose effect. The most common reasons for discontinuation were: injection site reactions, alcoholism (i.e., lack of efficacy), nausea, pregnancy, abnormal LFTs, and suicide-related AEs. There was a slightly higher incidence of dropout due to suicidal behavior for the drug-treated vs. the placebo-treated subjects, 0.9% vs. 0%, respectively). There was also a slightly higher incidence of dropout for depression, 0.3% vs. 0% for the drug vs. placebo-treated subjects, respectively. Neither of these events appeared to be dose-related, and the percentage of subjects dropping out for depression was highest in subjects treated with oral naltrexone.

Serious Adverse Events

Suicide-related serious AEs were reported more frequently in the drug-treated subjects compared to the placebo-treated subjects (1.4% vs. 0%, respectively). One subject in the 380-mg treatment group developed a severe injection site reaction described as necrosis requiring fairly extensive tissue excision. Histopathological evaluation of the excised tissue documented a "hypersensitivity reaction." One subject treated with 380-mg Vivitrol™ developed apparent eosinophilic pneumonia not responsive to antibiotics, but responsive to steroid treatment.

Common Adverse Events

The following gastrointestinal adverse events occurred more frequently in the Vivitrol™-treated subjects: nausea, vomiting, diarrhea, abdominal pain, dry mouth, flatulence/bloating, decreased appetite and decreased weight. Additional adverse events that occurred with greater frequency in Vivitrol™-treated subjects were: asthenia, injection site reactions, headache, dizziness, somnolence/sedation, muscle cramps, arthralgia, back pain, rash, angioedema/urticaria, anxiety, and depression and/or suicidal ideation.

While abnormal LFTs occurred with slightly greater frequency in the drug-treated subjects, the rates were comparable for the Vivitrol™-treated subjects and the oral naltrexone-treated subjects. Injection site reactions in the placebo-treated subjects were

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