

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-897

MEDICAL REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

DIVISION DIRECTOR'S APPROVAL MEMO

DATE: April 13, 2006

DRUG: Vivitrol™ (naltrexone for extended-release injectable suspension)

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 Vivitrol™ (naltrexone for extended-release injectable suspension)¹ on March 31, 2005. An approvable letter was issued on December 23, 2005. The letter noted that the sponsor would need to address the following issues prior to approval:

- the absence of Reproductive Toxicology and Carcinogenicity studies to support the clinical use of the product
- an absence of evidence that the product is safe and effective in patients who had not achieved abstinence prior to the initiation of treatment (see Division Director's Approvable Memo, dated December 23, 2005)

The sponsor has responded to these concerns by agreeing to perform post-marketing studies to assess the deficiency listed in the first bullet, and by agreeing to language in the label that will limit the indicated use of the product to "...patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment..."

¹ Vivitrol™ will be marketed in a kit.

Most of the subjects in the efficacy studies achieved initial abstinence through participation in a treatment program or via medical detoxification. There were no subjects who maintained abstinence in the setting of no continued available alcohol. Therefore, Drs. Kashoki and Winchell have recommended that the sponsor perform a post-marketing study to assess the efficacy of Vivitrol™ in patients who are abstinent “by virtue of hospitalization or other mechanism to limit access to alcohol” as these patients are likely to differ in regard to their motivation to stop drinking compared to patients who stop drinking in spite of access to alcohol. The sponsor has agreed to perform this study.

Drs. Kashoki and Winchell have reviewed the updated safety data in this submission and have determined that there are no new safety concerns that would impact the risk to benefit ratio of the product, when compared to the safety data analyzed in the initial application. However, they did find an increase in creatinine phosphokinase (CPK) serum levels with prolonged exposure and have recommended addition of these data to the product label. No serious adverse events were associated with these CPK elevations.

Discussion:

The sponsor has adequately addressed the concerns noted in the approvable letter. Of note, however, the absence of Reproductive Toxicology and Carcinogenicity data to fully cover the range of expected human exposure to naltrexone and to the polylactide-co-glycolide vehicle will not be fully elucidated at the time of approval and initial patient exposure. Nevertheless, the available data on reproductive toxicity indicates a low risk, the risk is certainly no more significant than the risk of fetal alcohol syndrome, and this risk can be mitigated by appropriate cautionary language in the product label until further data is available. There is also no evidence to suspect that the carcinogenic effects of the product are of unusual potential potency, and the absence of complete data to fully assess the long-term carcinogenic potential can be explicated in the label, again until further data is available. While our response to the initial application was that these studies should be completed prior to approval, this decision was partially based on the likelihood that the sponsor would be completing further clinical studies to support their proposed indication and, thus, the development program would allow for an adequate period of time to complete the preclinical studies prior to approval. However, the sponsor has proposed an alternate indication that we find acceptable and that will not require additional clinical studies. This new indication limits treatment to the subpopulation of alcoholic patients who will have achieved abstinence prior to treatment with Vivitrol™, the subpopulation that has been demonstrated to clearly benefit from treatment with this product. In light of this new development, and as alcoholism is a serious disease with significant associated morbidity and mortality, and a devastating impact on patients, families and the public health, we must reconsider the overall risk to benefit analysis upon which this application rests. Vivitrol™ is likely to provide alcoholic patients with a higher level of compliance compared to the currently approved treatments and, thus, an improvement in the likelihood that they will be able to successfully maintain abstinence.

As such, it is acceptable to garner the remaining data necessary to fully elucidate the toxicity of this product in the post-marketing setting.

Action: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

MEMORANDUM

DATE: April 11, 2006

TO: File, NDA 21-897

FROM: Celia Jaffe Winchell, M.D.
Medical Team Leader

RE: NDA 21-897
Response to Approvable Action
Letter Date 2/14/2006

I concur with Dr. Kashoki's review of the resubmission of this application and her recommendations.

In our original action letter conveying the Approvable decision on the application, we advised Alkermes that:

You have not provided evidence of efficacy of Vivitrol in alcohol-dependent patients who are actively drinking at the time of treatment initiation. —

propose labeling to restrict the use of the product to alcohol-dependent patients who have refrained from drinking — prior to treatment initiation.

Note that if you elect this latter option, we would expect you to conduct a post-approval study to determine whether Vivitrol is effective in patients whose pre-treatment abstinence is enforced (i.e. via hospitalization) rather than spontaneous (as was the case with the population studied in your efficacy trial, ALK21-003).

In this resubmission, Alkermes has elected the option of labeling the product for patients abstinent at the time of treatment initiation. However, they disagreed with the

requirement that a _____ and provided a reasonable rationale for deleting this _____ requirement. In addition, they correctly took issue with the term _____ to describe the abstinence of the study participants, many of whom had achieved initial abstinence through participation in a program of treatment and/or medical detoxification. The more appropriate descriptor of this population was that they had maintained abstinence in an outpatient setting (i.e., with access to alcohol) prior to treatment initiation; indeed, this was true of all of the subjects in question, as confirmed by Alkermes in a submission dated 3/10/2006 (sequence 0044).

Therefore, we have arrived at agreement regarding the appropriate description of the target population as "patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL." However, having elected this option, Alkermes will also be asked to agree to conduct a post-marketing study to determine whether Vivitrol is effective in patients who are abstinent by virtue of hospitalization or other mechanism to limit access to alcohol, rather than patients who are abstinent in spite of access to alcohol. As these populations are likely to differ with respect to level of motivation and/or alcoholism severity, this is a relevant question important to clinicians deciding whether or not patients being discharged from alcohol-free settings would benefit from treatment with Vivitrol upon discharge.

Consultation with the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety led to certain other modifications in the directions for use and other aspects of the labeling. However, some recommendations from DMETS were not implemented. DMETS questioned the need for multiple needles in the dosing kit. These are deemed necessary because, per the chemistry reviewer, Dr. Jila Boal, a short needle is needed for preparation to prevent aspiration of air into the syringe as the vial containing diluent has a small volume of liquid in it. The longer needles are needed for intramuscular injection. Although clogging of the needle was not a major problem in trials, it seems prudent to provide an extra needle for drug administration to ensure that a needle tested with the product (with the necessary lumen size to allow passage of the product) will be used. DMETS also recommended the inclusion of the final mg/ml concentration of the suspension; however, as the dosing for this product is essentially unit of use, this does not seem necessary and could cause confusion. Furthermore, the vial label for the microspheres and the carton label for the kit contain text reading, "upon reconstitution with 3.4 ml diluent, each ml will contain 95 mg of naltrexone." Therefore, the information is already included in the packaging.

In addition, as recommended by Dr. Lee of the Division of Pulmonary and Allergy Products who provided consultation during the initial review cycle, Alkermes will be asked to develop tests to detect allergy to the components of their product, with an eye towards identifying patients at risk for the serious, possibly allergy-mediated events noted during clinical trials, such as eosinophilic pneumonia and serious injection site reactions.

Since the completion of Dr. Kashoki's review, Alkermes also submitted additional information concerning study participants with CPK abnormalities; these abnormalities were generally isolated and transient and were not associated with symptoms or with concomitant creatinine elevations; no subject with extreme CPK values had an SAE reported in association with these findings.

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/s/

Celia Winchell
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2nd Cycle

CLINICAL REVIEW

Application Type N 21-897
Submission Number 000

Letter Date February 14, 2006
Stamp Date February 14, 2006
PDUFA Goal Date April 14, 2006

Reviewer Name Mwango Kashoki, MD, MPH
Review Completion Date April 4, 2006

Established Name: Naltrexone for extended-release
injectable suspension

Trade Name Vivitrol
Therapeutic Class Opioid antagonist
Applicant Alkermes

Priority Designation P

Formulation: Naltrexone long-acting (depot) injection
Dosing Regimen 380 mg IM q month
Indication Alcohol dependence
Intended Population Alcohol dependent adults

Table of contents

| | | |
|-------|--|----|
| 1 | Executive Summary | 3 |
| 2 | Background | 3 |
| 3 | NDA History | 4 |
| 3.1 | Review of non-clinical data | 4 |
| 3.2 | Review of clinical efficacy | 4 |
| 3.3 | Review of clinical safety | 5 |
| 3.4 | Regulatory action | 6 |
| 4 | Applicant's Response to Approvable Action Letter | 7 |
| 5 | Safety Update | 9 |
| 5.1 | Exposure | 9 |
| 5.2 | Adverse events | 12 |
| 5.2.1 | Deaths | 12 |
| 5.2.2 | Serious adverse events | 12 |
| 5.2.3 | Significant adverse events..... | 12 |
| 5.2.4 | Common adverse events | 12 |
| 5.3 | Discontinuations due to adverse events | 14 |
| 6 | Review of the Proposed Product Label..... | 14 |
| 6.1 | Review of clinically-related sections | 15 |
| 6.1.1 | “Clinical Studies” section | 15 |
| 6.1.2 | “Indications and Usage” section | 17 |
| 6.1.3 | “Warnings” section | 18 |
| 6.1.4 | “Information for Patients” section | 19 |
| 6.1.5 | “Adverse Reactions” section..... | 20 |
| 6.1.6 | “Dosage and Administration” section..... | 22 |
| 6.2 | Review of nonclinical-related sections | 26 |
| 7 | Review of the Proposed Patient Package Insert..... | 26 |
| 8 | Conclusions..... | 29 |
| 9 | Recommended Regulatory Action | 29 |
| 10 | Appendix..... | 30 |
| 10.1 | Appendix 1: Number (%) SAEs after 6 months | 30 |
| 10.2 | Appendix 2: Most common AEs after 6 months | 36 |
| 10.3 | Appendix 3: Discontinuations due to AEs..... | 42 |
| 10.4 | Appendix 4: Subjects who shifted from normal CPK at baseline to high | 46 |

1 Executive Summary

NDA 21-897 for Vivitrol (naltrexone for extended-release injectable suspension) was re-submitted by Alkermes on February 14, 2006. Vivitrol is a new depot formulation of naltrexone that is intended to treat alcohol dependence in adults. The application was initially submitted on March 31, 2005, and was issued an "approvable" action based on limited demonstration of efficacy and inadequate non-clinical data regarding carcinogenicity and reproductive toxicology. The current submission is deemed a complete response to the "approvable" letter.

Alkermes has adequately addressed the clinical deficiency by proposing labeling to restrict the use of Vivitrol to alcohol-dependent patients who are not actively drinking at the time of treatment initiation. Therefore, this review was primarily an assessment of the updated safety data, as well as the revised product label and patient package insert.

The updated safety database did not identify any new adverse effects of Vivitrol that were not previously identified. However, the update showed an increase in creatinine phosphokinase (CPK) with prolonged dosing. I recommend inclusion of these data in the product label.

Overall, Alkermes agreed with the Division's revisions to the proposed product label. The most notable counter-proposal to the revisions was regarding the "indications and usage" section. Alkermes sought to alter language describing the intended treatment population, removing references to _____ and a _____. The Applicant's rationale was deemed acceptable.

The patient package insert was completely rewritten _____, and to reflect the warnings and precautions identified during the NDA review.

Overall, therefore, the data and the submission are adequate and the application can be approved.

2 Background

Naltrexone for extended release injectable suspension (Vivitrol®) is a new intramuscular depot formulation of naltrexone. Naltrexone is a non-selective opioid antagonist with no agonist activity, and an oral formulation of the drug is currently approved for use in opiate dependence and alcohol dependence.

The Vivitrol formulation is comprised of extended-release microspheres of naltrexone base encapsulated in polylactide-co-glycolide (PLG), mixed in a 75:25 ratio. The naltrexone is the active ingredient. PLG is a biodegradable medical polymer which is used in several FDA-approved products. The microspheres are suspended in a diluent and the mixture is injected intramuscularly (IM).

- Drug established name: Naltrexone for extended release injectable suspension
- Chemical name: Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-(5 α)
- Proposed trade name: Vivitrol
- Drug class: non-selective opioid antagonist
- Proposed indication: Treatment of alcohol dependence, as part on an appropriate program for alcohol dependence
- Dose: 380-mg IM q month
 - Injections are to be administered by a health care professional. Injections are to be to the lateral aspect of the gluteal muscle, alternating buttocks with each administration.
- Age groups: Adults
 - Studies in children waived
 - Studies in adolescents deferred

3 NDA History

The initial NDA for Vivitrol was submitted on March 31, 2005. The indication sought was treatment of alcohol dependence, as part of an appropriate program for alcohol dependence, in adults who were — abstinent from drinking _____ at treatment initiation.

3.1 Review of non-clinical data

Alkermes submitted the NDA under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, citing as basis for the safety of Vivitrol the Agency's previous finding of safety of oral naltrexone, animal studies conducted using Vivitrol, and information from published literature of the safety of naltrexone. Review of the NDA found that Alkermes further referenced information from other approved products and the published literature regarding carcinogenicity, reproductive toxicology and genetic toxicology data on naltrexone and the PLG microspheres. However, no such studies were conducted using the final Vivitrol formulation. Therefore the referenced data were inadequate to fulfill the nonclinical requirements of the Vivitrol NDA, and additional data regarding the carcinogenicity and reproductive toxicology of Vivitrol were necessary.

3.2 Review of clinical efficacy

A single Phase 3 trial was submitted in support of efficacy of Vivitrol. The trial enrolled 627 patients, and 624 of whom took at least one dose of study drug. Patients were randomized to one of three groups: Vivitrol 380-mg (n = 205), Vivitrol 190-mg (n = 210), and placebo (n = 214). All patients participated in a psychosocial management program. Treatment duration was 6 months.

The Applicant's primary efficacy endpoint was the "event rate of heavy drinking", and was analyzed using a multiple event time analytic approach. This novel endpoint was intended to evaluate both the number and the timing of drinking events, and Alkermes demonstrated efficacy based on this endpoint. However, the Division deemed the endpoint inadequate for several reasons. First, the endpoint is not clinically intuitive – the clinical meaning of a reduction in the "event rate" of heavy drinking is not clear. Also, the magnitude of a reduction in the event rate of heavy drinking that is associated with clinical improvement is not known. Finally, the endpoint is a result of a group mean analysis, and does not provide information on the effects of treatment on an individual patient level.

Based on recent (unpublished) data from the National Institute of Alcohol Abuse and Alcoholism which found that sustained absence of heavy drinking over the treatment period was associated with few drinking consequences, the Division considered 'absence of heavy drinking' as the optimal definition for treatment success in alcoholism trials. 'Heavy' drinking is ≥ 4 drinks/day (women), and ≥ 5 drinks/day (men).

The Division's re-analysis of the efficacy data found that overall there were no numerical or statistical differences between either dose of Vivitrol and placebo with respect to the proportion of patients who were able to refrain from heavy drinking during the treatment period. However, when treatment response was evaluated based on drinking status at study initiation (i.e. actively drinking vs. abstinent from any drinking), the proportion of patients meeting the definition of treatment success greatly increased, and a difference between the Vivitrol and placebo groups was suggested for patients abstinent at baseline. The efficacy results are summarized in the table below:

| Actual number of heavy drinking days* per month | N (%) | | | P value | |
|--|---------|---------|---------|-------------------|--------------------|
| | Placebo | 190 mg | 380 mg | 190mg vs. placebo | 380-mg vs. placebo |
| All patients (abstinent and non-abstinent at baseline) | | | | | |
| 0 | 11 (5%) | 15 (7%) | 14 (7%) | 0.4325 | 0.5107 |
| Patients abstinent at baseline | | | | | |
| 0 | 2 (11%) | 6 (35%) | 6 (35%) | 0.1212 | 0.1212 |

* "Heavy drinking day" is defined as ≥ 4 drinks/day (women), and ≥ 5 drinks/day (men).

In addition, when the "event rate" analysis was repeated using these subgroups, it was apparent that the efficacy shown in the primary analysis was driven almost exclusively by the subgroup of patients that was abstinent at baseline. Thus, even using the protocol-specified analytic approach, efficacy was not demonstrated for those patients who were actively drinking at baseline.

3.3 Review of clinical safety

Alkermes partly relied on the Agency's previous finding of safety of oral naltrexone to support its NDA for Vivitrol. Additional safety information on naltrexone was based on

propose labeling to restrict the use of the product to alcohol-dependent patients who have refrained from drinking — prior to treatment initiation.

Note that if you elect this latter option, we would expect you to conduct a postapproval study to determine whether Vivitrol is effective in patients whose pretreatment abstinence is enforced (i.e. via hospitalization) rather than spontaneous (as was the case with the population studied in your efficacy trial, ALK21-003).

2. Provide pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data in the product labeling. In the absence of adequate bridging data, the following nonclinical studies would have to be conducted:
 - a. a Segment I reproductive and developmental toxicology study including toxicokinetic data in a single species with the final drug product formulation;
 - b. Segment II reproductive and developmental toxicology studies in two species including toxicokinetic data with the final drug product formulation;
 - c. a Segment III reproductive and developmental toxicology study including toxicokinetic data with the final drug product formulation; and
 - d. carcinogenicity assessment in two species using the final drug product formulation.”

Additional clinical comments that were not approvability issues were:

- “To further evaluate the allergenic potential of Vivitrol, conduct a trial to ascertain whether patients develop naltrexone-specific, naltrexone-carboxymethylcellulosespecific, and carboxymethylcellulose-specific antibodies (IgG, IgM, and IgE1) following Vivitrol administration. Evaluate whether development of these specific antibodies is associated with adverse events of urticaria and angioedema.
- Conduct in vitro CYP inhibition studies using conventional CYP substrates and validated analytical methodology.
- Conduct in vitro studies in human hepatocytes to evaluate the potential of naltrexone to induce CYP3A4 and CYP1A2.”

4 Applicant’s Response to Approvable Action Letter

Response to the clinical deficiency

Alkermes has agreed to the Agency’s alternate recommendation to restrict the use of Vivitrol to a subgroup of alcohol-dependent patients: “patients who are able to abstain from alcohol prior to treatment initiation.” Alkermes has modified the proposed product label to reflect the treatment population.

Alkermes has also committed to conducting a post-approval study to determine whether Vivitrol is efficacious in patients whose pretreatment abstinence is enforced (e.g. via hospitalization) or maintained despite access to alcohol in the outpatient setting.

Response to the non-clinical deficiency

Refer to the Pharmacology/Toxicology review for details.

Believing itself to have adequately addressed the identified NDA deficiencies, the Applicant has submitted a revised product label and patient package insert for review, and is seeking additional Agency action on the NDA.

Safety Update

As requested in the Action Letter, Alkermes has provided an update of the safety data from all clinical studies, and an evaluation of how the data compare to those in the original NDA.

Revisions to the product label

The major clinical changes to the initially that the *Division* proposed for product label are listed below. (Refer to the Pharmacology/Toxicology review for details regarding the changes proposed for the non-clinical sections of the label)

- The clinical studies section was rewritten to describe the alternate endpoint used to describe efficacy, as well as the magnitude of efficacy observed. The characteristics of the population studied (e.g. individuals abstinent at baseline) was emphasized. The Applicant's _____ were deleted, _____
Also deleted were _____
/ / /
- The indications section was rewritten to describe the specific population in which efficacy was shown. The requirement for concurrent participation in an appropriate psychosocial management program was included.
- The contraindications section was modified as follows: statements stating that Vivitrol is contraindicated in the following individuals
 - Persons who have failed the naloxone challenge test or who has a positive urine screen for opioids; and
 - Persons with acute hepatitis or liver failure
- Warnings describing the following risks were added:
 - Hepatotoxicity
 - Eosinophilic pneumonia
 - Unintended precipitation of opioid withdrawal with Vivitrol
 - Potential overdose with attempts to overcome naltrexone blockade
- The precautions section was expanded to describe

- The risk of injection site reactions
- The need for monitoring for emergence of depressive symptoms, and suicidal ideation/attempt following treatment with Vivitrol

Alkermes accepted the majority of the Division's revisions to the product label, with minor editorial corrections. The most significant counter proposals to the label language were with respect to the:

- a) Clinical studies section – The Applicant proposed inclusion of _____
- b) Indications and usage section – Alkermes removed references to ' _____ , as well as the _____
- c) Dosage and administration section – Alkermes modified the instructions regarding drug preparation using the kit components

Alkermes did not propose any major revisions to the patient package insert.

5 Safety Update

The Safety Update Report (SUR) in this NDA resubmission contains new information from two ongoing long-term extension studies. There is no new information from clinical pharmacology studies or blinded, short-term trials.

The resubmission incorporates data from the ongoing studies ALK21-006-EXT and ALK21-010, through August 31, 2005. Study ALK21-006-EXT is an extension of ALK21-006, therefore subjects in the –EXT study are a subset of the ALK21-006 (previously described in the original submission). Similarly, subjects in ALK21-010 are a subset of the ALK21-003 population (also described in the original submission).

Alkermes reported safety data using three categories:

- **Application data** – These are the data as originally reported in the NDA
- **SUR data** – Reflect data obtained during the SUR period (i.e. 9/1/04 through 8/31/05)
- **Combined > 6 month data** – Represent the most updated Vivitrol safety profile for subjects with > 6 months' exposure (i.e. incorporates the SUR data)

5.1 Exposure

A total of 1,232 subjects have participated in 7 primary clinical trials and 3 extension studies of Vivitrol suspension. No new subjects were enrolled during the SUR period.

As of 31 August 2005, 1065 subjects have been treated with Vivitrol: 84 healthy subjects, 12 with hepatic impairment but who were not substance dependent, 838 with alcohol

dependence, 27 non-dependent opioid users, and 104 who were either opiate dependent or mixed alcohol-opiate dependent.

Table 1 (following page) shows the cumulative exposure to Vivitrol. Altogether, 942 alcohol and/or opiate dependent patients have received at least one dose of Vivitrol. A total of 408 subjects have received at least 6 doses (i.e. 6 months of exposure) of Vivitrol suspension at 380 mg/dose, 232 have received at least 12 doses (1 year), and 61 have received at least 24 doses (2 years). Three subjects have received monthly doses of Vivitrol 190 mg for 43 months, and 1 subject has received monthly 380 mg injections for 42 months.

Table 1: Overall cumulative exposure to Vivitrol – Combined data

| Study | At Least 1 Injection | | At Least 6 Injections | | At Least 12 Injections | | At Least 18 Injections | | At Least 24 Injections | | At Least 30 Injections | | At Least 36 Injections | |
|---------------------------|----------------------|-------|-----------------------|-------|------------------------|-------|------------------------|-------|------------------------|-------|------------------------|-------|------------------------|-------|
| | 190mg | 360mg | 190mg | 360mg | 190mg | 360mg | 190mg | 360mg | 190mg | 360mg | 190mg | 360mg | 190mg | 360mg |
| ALK21-002* | | 25 | | | | | | | | | | | | |
| ALK21-003 | 210 | 205 | 137 | 130 | | | | | | | | | | |
| ALK21-003EXT ¹ | 55 | 60 | 40 | 32 | 98 | 91 | 59 | 46 | | | | | | |
| ALK21-010 ² | | | | | | | 12 | 17 | 44 | 49 | 29 | 35 | 16 | 15 |
| ALK21-006 ³ | | 371 | | 232 | | 138 | | | | | | | | |
| ALK21-006EXT ³ | | 16 | | 14 | | 3 | | 62 | | 12 | | | | |
| Subtotal | 265 | 677 | 177 | 408 | 98 | 232 | 62 | 125 | 44 | 61 | 28 | 35 | 16 | 15 |
| Grand Total | 942 | 585 | 330 | 187 | 105 | 64 | 31 | | | | | | | |

* Vivitrol dose for 25 subjects in ALK21-002 was 400mg.

¹ ALK21-003EXT is the extension of ALK21-003.

² ALK21-010 is the extension of ALK21-003EXT.

³ ALK21-006EXT is the extension of ALK21-006.

Note: Table indicates the number of subjects who achieved dosing criterion stated in the column heading first time with the cumulative number of Vivitrol doses received.

(Source: Applicant's Summary of Clinical Safety, Table 2.2, p. 14)

5.2 Adverse events

Overall, no new safety concerns have emerged since the 120-day Safety Update.

5.2.1 Deaths

No new deaths have occurred since the 120- Day Safety Update.

5.2.2 Serious adverse events

The frequency of SAEs in patients with at least 6 months of drug exposure was increased at the end of the SUR period (10%), compared to the original NDA (5%) (Appendix 1). The majority of this increase is due to a rise in reports of alcoholism, depression, and suicidal behavior. The original NDA reported <1% of subjects with 6 or more months of exposure experiencing serious alcoholism; the incidence was 2% at the end of the SUR period. Also, at the end of the SUR period there were 6 patients (1%) with serious suicidal behavior (completed suicide, suicide attempt, suicidal ideation), compared to 2 patients (<1%) in the original NDA. No serious events of depression were reported in the original NDA, however 2 patients (<1%) had experienced this at the end of the SUR period.

Alkermes argues that the increased incidence of these particular SAEs is not unusual because alcohol dependence is a known risk factor for depression and suicide-related events, and the increased incidence of these events was likely with extended monitoring.

Comment: While the Applicant's rationale for the increase is plausible, it remains possible that prolonged exposure to naltrexone's antagonistic effects mu-opioid receptor increases the risk of dysphoria. However, without a placebo group for comparison, the clinical significance of the increase in these SAEs cannot be fully determined.

Otherwise, the type and frequency of SAEs reported in the SUR are similar to those described in the initial NDA submission.

5.2.3 Significant adverse events

During the SUR period there no reports of

- Hepatotoxicity
- Eosinophilic pneumonia
- Angioedema or urticaria
- Serious injection site reactions (ISRs)
- Opiate overdose

5.2.4 Common adverse events

Combined > 6 month experience

The table in Appendix 3 summarizes the most common AEs (i.e., individual events occurring in at least 5% of subjects in any treatment group) after 6 months of treatment. The table compares the frequency of events noted in the original NDA to the frequency

of events through to August 31, 2005. It includes information from the completed open-label safety studies, ALK21-003EXT and ALK21-006.

Infections and infestations were the most common class of AEs, occurring in 43% of patients. Gastrointestinal disorders were the next common (28%), followed by psychiatric disorders (24%) and musculoskeletal and connective tissue disorders (23%). There was a similar incidence of general disorders and administration site conditions (22%), nervous system disorders (21%), as well as injury, poisoning, and procedural complications (20%). All other classes of AEs accounted for fewer than 20% of reported events.

Overall, the types AEs observed were similar to that reported in the original NDA. The frequency of certain AEs was higher in the SUR compared to the original NDA: increased creatinine phosphokinase (CPK) (16% vs. 10%); upper respiratory tract infections (13% vs. 9%); depression (9% vs. 5%); and headache (11% vs. 9%).

Comment: The initial NDA submission showed that, among the trials of 4-6 months' duration, there was a small, non-clinically significant increase in the mean CPK value for the Vivitrol 380 mg group after 24 weeks. The mean CPK values for the Vivitrol 190 mg, placebo, or oral naltrexone groups were relatively unchanged. However, analyses of outliers and shifts from normal to abnormal found that the Vivitrol 380-mg group had a slightly more patients (11%) than placebo (8%) shift from a normal CPK value at baseline to high value at Week 24. The oral naltrexone group had an even higher number (17%) of patients shift from normal to high CPK. I theorized that the reason for this is that elevated CPK is known to occur in patients with alcohol abuse. Another potential explanation is that elevated CPK is an adverse effect of naltrexone treatment.

In the studies of 4-6 months' exposure, there were 10 patients (10/1090, 0.9%) who had extreme (≥ 3 x upper limit of normal (ULN)) CPK values at Week 24: 4 (1.9%) patients in the placebo group, 3 (1.4%) patients in the 190-mg group, and 3 (0.5%) patients in the 380-mg group. Of the 10 patients, 4 had AE reports of elevated CPK, none of which was considered serious. There were 2 patients in the placebo group, and 1 each in the 190-mg and 380-mg Vivitrol groups. None of the reports of CPK elevations occurred in the setting of muscle injury, renal disease, infection, increased drinking, or any other potential cause of CPK increases. Thus I concluded that there was no clear reason for the CPK elevation apart from naltrexone (oral or depot) exposure.

Overall, with respect to the SUR data finding of increased CPK following long-term exposure, without a placebo group for comparison and in the absence of an obvious cause based on the short-term controlled trials, the clinical significance of the increase in CPK cannot be fully determined.

To determine the severity (i.e. range) of the reported CPK abnormalities, Alkermes was asked to tabulate the proportions of the patients in the trials of 4-6 months'

duration who had shifts in CPK from 'normal' at baseline to 'high' at study end, indicating the maximum CPK value obtained as well as the multiple of the ULN that the maximum value represented (Appendix 4; e-mail correspondence received March 30, 2006). The data showed that, for both the oral naltrexone and Vivitrol 380-mg groups, CPK abnormalities were most frequently in the range of 1-2 x ULN. However, there were reports of CPK abnormalities as high as 4x ULN for the oral naltrexone group, and 35 x ULN for the Vivitrol 380-mg group.

5.3 Discontinuations due to adverse events

At the end of the SUR period, total of 45 subjects (45/574, 8%) had experienced an AE that led to discontinuation after at least 6 months of treatment (Appendix 3). The most frequent categories of AEs that led to treatment discontinuation were "general disorders and administration site conditions" (11/574, 2%), psychiatric disorders (8/574, 1%) and gastrointestinal disorders (7 subjects, 1%).

Comment: The "psychiatric disorders" category of AEs included alcoholism. However, this particular event is more accurately described as lack of treatment efficacy.

With respect to individual AEs resulting in discontinuation, nausea was the most common (5 subjects, <1%), followed by injection site induration (4 subjects, <1%), injection site pain and liver function tests NOS abnormal (each 3 subjects, <1%), and headache, alcoholism, and eosinophilia (each 2 subjects, <1%). No other AE led to discontinuation for more than 1 subject.

The causes of discontinuation were similar to those listed in the original NDA.

6 Review of the Proposed Product Label

The proposed package insert and patient package insert were reviewed by this Division, the Division of Surveillance, Research, and Communication Support (DSCRCS), and the Division of Medication Errors and Technical Support (DMETS). The recommendations from DSCRCS and DMETS are incorporated into the Division's revisions of the product labeling.

Of note, DMETS recommended that the final milligram per milliliter (mg/mL) concentration after reconstitution of the microspheres in the diluent be shown on the package insert, as well as the carton and container. The reason for the recommendation is that it would allow practitioners to determine what volume of suspension is to be administered for the prescribed dose. However, because (1) the drug is provided in a unit-of-use package, (2) only one dose (380-mg) is to be administered, and (3) the entire dose is obtained from the single vial, addition of the mg/mL concentration to the packaging and label is *not* required prior to drug approval.

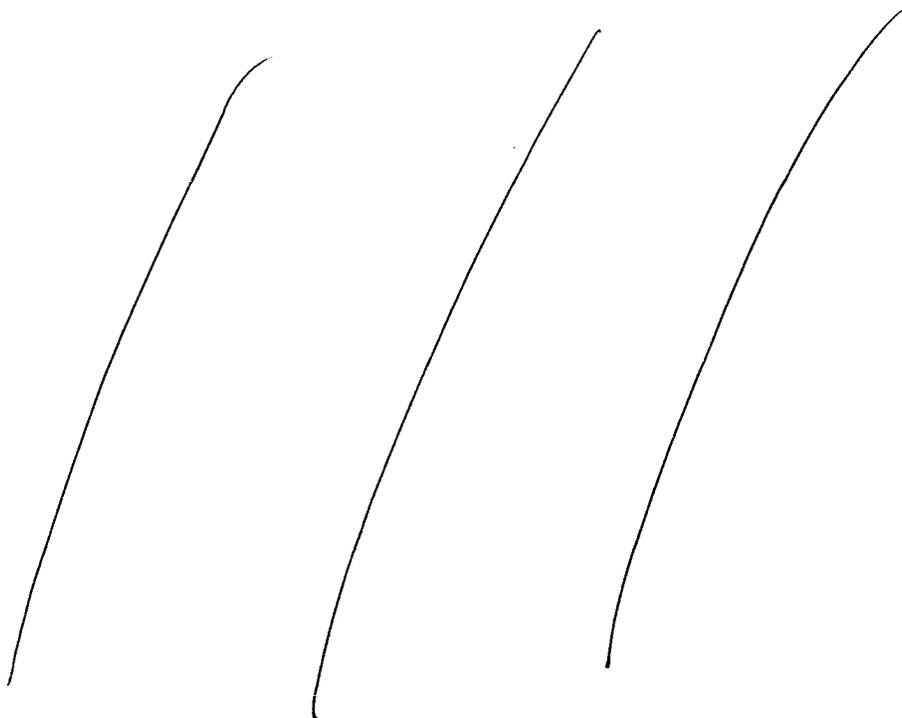
DMETS also commented on the provision of an extra 20 gauge needle for intramuscular administration of Vivitrol. A second needle is provided in case of clogging, and DMETS recommended that a larger bore needle be provided to prevent a third needle stick, in the event that both 20 gauge needles clog. The Division has previously addressed the issue of needle clogging with the Applicant (teleconference dated November 2, 2005). The Applicant explained that:

- Microsphere suspensions for injection have higher viscosity and greater particle size, and hence have the potential for needle clogs. Two approved microsphere based products are marketed with extra needles and have instructions to use a new needle in the event of a clog.
- In order to minimize needle gauge, Alkermes employed thin walled needles (1 1/2" 20G — safety needle) in its clinical trials, and will include these needles in the kit. These needles have thinner walls than standard needles allowing for a greater internal diameter than a standard 20G needle.

The Applicant's rationale for inclusion of an extra needle, as well as for use of the 20G — needle for administration, were found acceptable by the Division.

6.1 Review of clinically-related sections

6.1.1 "Clinical Studies" section

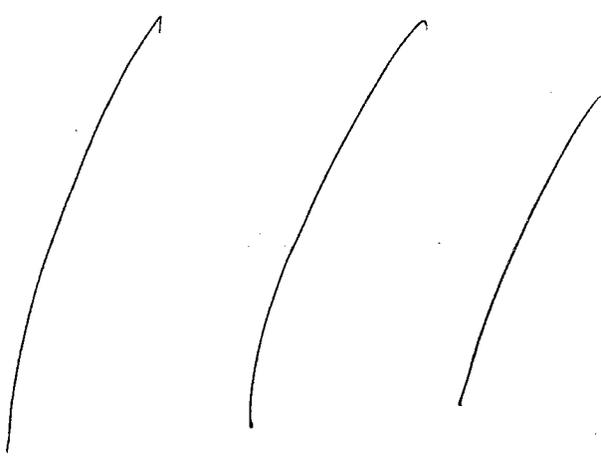


13 Page(s) Withheld

 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process



8 Conclusions

By restricting the use of Vivitrol to adult alcohol dependent patients who are not actively drinking at the start of treatment, Alkermes has adequately addressed the clinical deficiency as stated in the “approvable” action letter.

No new safety concerns have emerged from the updated safety information.

The proposed product label and patient package insert have been reviewed and revisions made. Agreement on the final wording will be reached through discussion with the Applicant.

9 Recommended Regulatory Action

The application can be approved.

10 Appendix

10.1 Appendix 1: Number (%) SAEs after 6 months

| System Organ Class (MedDRA) Preferred Term (MedDRA) | All Subjects | | Placebo to 196mg | | 196mg to 196mg | | Placebo to 380mg | |
|--|--------------|----------|------------------|----------|----------------|----------|------------------|----------|
| | NDA* | Updates* | NDA* | Updates* | NDA* | Updates* | NDA* | Updates* |
| No. of subjects dosed after 6 months | 572 | 574 | 55 | 55 | 102 | 102 | 60 | 60 |
| No. of subjects with an SAE | 28 (5) | 56 (10) | 2 (4) | 2 (4) | 13 (13) | 15 (12) | 2 (3) | 4 (7) |
| PSYCHIATRIC DISORDERS | | | | | | | | |
| Alcoholism | 7 (1) | 21 (4) | 2 (4) | 2 (4) | 2 (2) | 4 (4) | 0 | 2 (3) |
| Suicidal ideation | 3 (<1) | 9 (2) | 2 (4) | 2 (4) | 1 (<1) | 1 (<1) | 0 | 2 (3) |
| Depression | 2 (<1) | 3 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Drug dependence | 1 (<1) | 2 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Suicide attempt | 0 | 2 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Anxiety NEC | 1 (<1) | 2 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Completed suicide | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Confusion | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Mood disorder NOS | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| INFECTIONS AND INFESTATIONS | | | | | | | | |
| Pneumonia NOS | 2 (<1) | 5 (1) | 0 | 0 | 2 (2) | 3 (3) | 0 | 0 |
| Bronchitis acute NOS | 1 (<1) | 2 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Cellulitis | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastroenteritis NOS | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Meningitis viral NOS | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Pneumonia bacterial NOS | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Staphylococcal infection NOS | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| GASTROINTESTINAL DISORDERS | | | | | | | | |
| Abdominal pain NOS | 3 (<1) | 5 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Abdominal pain upper | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Colitis ischaemic | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Ileus paralytic | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Oesophageal ulcer haemorrhage | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | | | | | | |
| Heat exhaustion | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Laceration | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |

(table continues on next page)

(Source: Applicant's Summary of Clinical Safety, Table 2.13, p. 57-62)

Appendix 1: Number (%) SAEs after 6 months (all data compared with NDA) (continued)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | Vivitsol 380mg to 380mg (ALK21-006EXT and ALK21-010) | | Vivitsol 380mg (ALK21-006 and ALK21-006EXT) | | Oral Maltrepone (ALK21-006) | | Oral 50 380mg ALK21-006EXT Update* | |
|---|--|---------|---|---------|--------------------------------|---------|---|---------|
| | NEA* | Update* | NEA* | Update* | NEA* | Update* | NEA* | Update* |
| No. of subjects dosed after 6 months | 115 | 115 | 204 | 206 | 56 | 56 | 16 | 16 |
| No. of subjects with an SAE | 4 (3) | 6 (5) | 5 (2) | 32 (11) | 2 (6) | 4 (11) | 2 (13) | 2 (13) |
| PSYCHIATRIC DISORDERS | | | | | | | | |
| Alcoholism | 0 | 0 | 2 (<1) | 8 (4) | 1 (3) | 4 (11) | 0 | 0 |
| Suicidal ideation | 0 | 0 | 0 | 2 (<1) | 0 | 2 (6) | 0 | 0 |
| Depression | 0 | 0 | 1 (<1) | 2 (<1) | 0 | 0 | 0 | 0 |
| Drug dependence | 0 | 0 | 0 | 1 (<1) | 0 | 1 (3) | 0 | 0 |
| Suicide attempt | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 1 (3) | 0 | 0 |
| Anxiety NEC | 0 | 0 | 0 | 2 (<1) | 0 | 0 | 0 | 0 |
| Completed suicide | 0 | 0 | 0 | 0 | 1 (3) | 0 | 0 | 0 |
| Confusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mood disorder NOS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| INFECTIONS AND INFESTATIONS | | | | | | | | |
| Pneumonia NOS | 0 | 0 | 0 | 5 (2) | 0 | 0 | 0 | 0 |
| Bronchitis acute NOS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Cellulitis | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Gastroenteritis NOS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Meningitis viral NOS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Pneumonia bacterial NOS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Staphylococcal infection NOS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| GASTROINTESTINAL DISORDERS | | | | | | | | |
| Abdominal pain NOS | 2 (2) | 2 (2) | 0 | 1 (<1) | 0 | 0 | 1 (6) | 1 (6) |
| Abdominal pain upper | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Colitis ischemic | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Ileus paralytic | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Oesophageal ulcer haemorrhage | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 1 (6) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | | | | | | |
| Heat exhaustion | 0 | 0 | 1 (<1) | 3 (1) | 0 | 0 | 0 | 0 |
| Laceration | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 |

(Source: Applicant's Summary of Clinical Safety, Table 2.13, p. 57-62)

(table continues on next page)

Appendix 1: Number (%) SAEs after 6 months (all data compared with NDA) (continued)

Vivitrol (ALK21-003Ext and ALK21-010)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | All Subjects | | Placebo to 180mg | | 180mg to 180mg | | Placebo to 360mg | |
|--|--------------|---------|------------------|---------|----------------|---------|------------------|---------|
| | NDA* | Update* | NDA* | Update* | NDA* | Update* | NDA* | Update* |
| Limb injury NOS | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Postoperative fever | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Road traffic accident | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 3 (<1) | 4 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Chest pain | 2 (<1) | 4 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Fyrexia | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CARDIAC DISORDERS | 3 (<1) | 3 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Angina pectoris | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Angina unstable | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac failure congestive | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Coronary artery atherosclerosis | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 1 (<1) | 3 (<1) | 0 | 0 | 0 | 0 | 1 (2) | 1 (2) |
| Aseptic necrosis bone | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Bunion | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Intervertebral disc degeneration NOS | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 1 (2) | 1 (2) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 1 (<1) | 3 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Asthma NOS | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Bronchospasm NOS | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Emphysema | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| VASCULAR DISORDERS | 1 (<1) | 3 (<1) | 0 | 0 | 1 (<1) | 2 (2) | 0 | 0 |
| Deep venous thrombosis NOS | 0 | 2 (<1) | 0 | 0 | 0 | 2 (2) | 0 | 0 |
| Hypertension NOS | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Pulmonary embolism | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |

(Source: Applicant's Summary of Clinical Safety, Table 2.13, p. 57-62)

Appendix 1: Number (%) SAEs after 6 months (all data compared with NDA) (continued)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | VIVITROL 380MG TO 380MG (ALK21-005EXT and ALK21-010) | | VIVITROL 380MG (ALK21-006 and ALK21-005EXT) | | Oral Naltrexone (ALK21-006) | | Oral to 380mg, ALK21-005EXT | |
|--|--|---------|---|---------|--------------------------------|---------|-----------------------------------|---------|
| | NDA* | Update* | NDA* | Update* | NDA* | Update* | NDA* | Update* |
| Limb injury NOS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Postoperative fever | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Road traffic accident | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION | 0 | 2 (2) | 2 (<1) | 1 (<1) | 0 | 0 | 0 | 0 |
| SITE CONDITIONS | 0 | 2 (2) | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 |
| Chest pain | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 |
| Pyrexia | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 |
| CARDIAC DISORDERS | 1 (<1) | 1 (<1) | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 |
| Angina pectoris | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Angina unstable | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Cardiac failure congestive | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Coronary artery atherosclerosis | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 1 (5) | 0 |
| Aseptic necrosis bone | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (5) |
| Bunion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intervertebral disc degeneration NOS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 0 | 0 | 0 | 2 (<1) | 0 | 0 | 0 | 0 |
| Asthma NOS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Bronchospasm NOS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Emphysema | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| VASCULAR DISORDERS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Deep venous thrombosis NOS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypertension NOS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Pulmonary embolism | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

(table continues on next page)

(Source: Applicant's Summary of Clinical Safety, Table 2.13, p. 57-62)

Appendix 1: Number (%) SAEs after 6 months (all data compared with NDA) (continued)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | VIVITROL (ALK21-093EXT and ALK21-010) | | | | | |
|---|---------------------------------------|------------------|----------------|------------------|------|---------|
| | All Subjects | Placebo to 190mg | 190mg to 190mg | Placebo to 380mg | NDA* | Update* |
| HEPATOBIILIARY DISORDERS | | | | | | |
| Cholecystitis acute NOS | 2 (<1) | 0 | 2 (2) | 0 | 0 | 0 |
| Cholelithiasis | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 |
| Hepatitis acute | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 |
| METABOLISM AND NUTRITION DISORDERS | | | | | | |
| Dehydration | 2 (<1) | 1 (2) | 0 | 0 | 0 | 0 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (IMCL CYSTS AND POLYPS) | | | | | | |
| Breast cancer NOS | 0 | 0 | 0 | 0 | 0 | 0 |
| Pancreatic carcinoma NOS | 1 (<1) | 0 | 0 | 0 | 0 | 0 |
| SOCIAL CIRCUMSTANCES | | | | | | |
| Drug abuser NOS | 1 (<1) | 0 | 0 | 0 | 0 | 0 |
| NERVOUS SYSTEM DISORDERS | | | | | | |
| Cerebral arterial aneurysm | 0 | 0 | 0 | 0 | 0 | 0 |
| SURGICAL AND MEDICAL PROCEDURES | | | | | | |
| Alcohol detoxification | 1 (<1) | 0 | 0 | 0 | 0 | 0 |
| Coronary arterial stent insertion | 0 | 0 | 0 | 0 | 0 | 0 |

(table continues on next page)

(Source: Applicant's Summary of Clinical Safety, Table 2.13, p. 57-62)

Appendix 1: Number (%) SAEs after 6 months (all data compared with NDA) (continued)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | Vivitrol 360mg to 360mg (ALK21-006Ext and ALK21-010) | | Vivitrol 360mg (ALK21-006 and ALK21-006Ext) | | Oral Naloxone (ALK21-006) | | Oral to 360mg ALK21-006Ext Update* | |
|---|--|---------|---|---------|------------------------------|---------|---|---------|
| | NDA* | Update* | NDA* | Update* | NDA* | Update* | NDA* | Update* |
| HEPATOBIILIARY DISORDERS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cholecystitis acute NOS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cholelithiasis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hepatitis acute | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| METABOLISM AND NUTRITION DISORDERS | 0 | 0 | 1 (<1) | 1 (<1) | 1 (<1) | 1 (<1) | 0 | 0 |
| Dehydration | 0 | 0 | 1 (<1) | 1 (<1) | 1 (<1) | 1 (<1) | 0 | 0 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL. CYSTS AND POLYPS) | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Breast cancer NOS | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Pancreatic carcinoma NOS | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| SOCIAL CIRCUMSTANCES | 0 | 0 | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Drug abuser NOS | 0 | 0 | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| NERVOUS SYSTEM DISORDERS | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Cerebral arterial aneurysm | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| SURGICAL AND MEDICAL PROCEDURES | 0 | 0 | 0 | 0 | 1 (<1) | 1 (<1) | 1 (3) | 0 |
| Alcohol detoxification | 0 | 0 | 0 | 0 | 0 | 0 | 1 (3) | 0 |
| Coronary arterial stent insertion | 0 | 0 | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |

* 'NDA' columns provide counts as reported with the original NDA, 'Update' columns are with data as of 8/31/2005.

† Subjects who were dosed in ALK21-006Ext are counted only once for the All Subject column at each row.

‡ Events with onset prior to first Vivitrol dose of ALK21-006Ext (if enrolled).

§ Events with onset after first Vivitrol dose of ALK21-006Ext.

¶ Note: Percentages are out of number of subjects dosed after 6 months.

(Source: Applicant's Summary of Clinical Safety, Table 2.13, p. 57-62)

10.2 Appendix 2: Most common AEs after 6 months

| System Organ Class (MedDRA) Preferred Term (MedDRA) | All Subjects | | | | | | | | | | | | | | | |
|--|------------------|---------|------|---------|----------------|---------|------|---------|------------------|---------|------|---------|----|----|----|----|
| | Placebo to 190mg | | | | 190mg to 190mg | | | | Placebo to 380mg | | | | | | | |
| | NDA# | Update# | NDA# | Update# | NDA# | Update# | NDA# | Update# | NDA# | Update# | NDA# | Update# | | | | |
| No. of subjects dosed after 6 months | 572 | 574 | 55 | 55 | 102 | 102 | 102 | 102 | 85 | 83 | 51 | 85 | 51 | 85 | 51 | 85 |
| No. of subjects with an AE | 396 | 467 | 467 | 467 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 |
| INFECTIONS AND INFESTATIONS | 179 | 245 | 245 | 245 | 47 | 47 | 47 | 47 | 47 | 47 | 47 | 47 | 47 | 47 | 47 | 47 |
| Upper respiratory tract infection NOS | 51 | 73 | 73 | 73 | 10 | 10 | 10 | 10 | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| Nasopharyngitis | 42 | 60 | 60 | 60 | 6 | 6 | 6 | 6 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| Sinusitis NOS | 19 | 28 | 28 | 28 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Influenza | 17 | 23 | 23 | 23 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Urinary tract infection NOS | 10 | 20 | 20 | 20 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Bronchitis NOS | 12 | 19 | 19 | 19 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Gastroenteritis viral NOS | 9 | 16 | 16 | 16 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Pneumonia NOS | 7 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Herpes simplex | 2 | 4 | 4 | 4 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Respiratory tract infection NOS | 1 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GASTROINTESTINAL DISORDERS | 124 | 161 | 161 | 161 | 18 | 18 | 18 | 18 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 |
| Nausea | 39 | 47 | 47 | 47 | 10 | 10 | 10 | 10 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Vomiting NOS | 15 | 23 | 23 | 23 | 1 | 1 | 1 | 1 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| Diarrhoea NOS | 13 | 20 | 20 | 20 | 1 | 1 | 1 | 1 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Toothache | 11 | 19 | 19 | 19 | 1 | 1 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Dyspepsia | 11 | 16 | 16 | 16 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Abdominal pain NOS | 10 | 13 | 13 | 13 | 0 | 0 | 0 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Abdominal pain upper | 11 | 10 | 10 | 10 | 0 | 0 | 0 | 0 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Gastritis alcoholic | 1 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Eructation | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Oesophageal ulcer haemorrhage | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PSYCHIATRIC DISORDERS | 91 | 138 | 138 | 138 | 17 | 17 | 17 | 17 | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| Depression | 29 | 50 | 50 | 50 | 8 | 8 | 8 | 8 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Insomnia | 28 | 41 | 41 | 41 | 4 | 4 | 4 | 4 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| Anxiety NEC | 17 | 30 | 30 | 30 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Alcoholism | 7 | 14 | 14 | 14 | 4 | 4 | 4 | 4 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Drug dependence | 1 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

(Source: Applicant's Summary of Clinical Safety, Table 2.6, p. 27 - 32)

Appendix 2: Most common AEs after 6 months (all data compared with NDA) (continued)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | Vivitrol 380mg to 380mg (ALK21-006EXT and ALK21-010) | | Vivitrol 380mg (ALK21-006 and ALK21-006EXT) | | Oral Maltrexone (ALK21-006) | | Oral to 380mg ALK21-006EXT | |
|--|--|---------|---|----------|--------------------------------|---------|----------------------------------|---------|
| | NDA* | Update* | NDA* | Update* | NDA* | Update* | NDA* | Update* |
| No. of subjects dosed after 6 months | 115 | 115 | 204 | 206 | 36 | 36 | 16 | 16 |
| No. of subjects with an AE | 93 (81) | 93 (81) | 102 (50) | 160 (79) | 20 (56) | 29 (81) | 10 (63) | 10 (63) |
| INFECTIONS AND INFESTATIONS | | | | | | | | |
| Upper respiratory tract infection NOS | 46 (49) | 49 (43) | 32 (16) | 76 (36) | 5 (17) | 12 (33) | 7 (44) | 7 (44) |
| Nasopharyngitis | 15 (13) | 15 (13) | 11 (5) | 22 (11) | 1 (3) | 2 (6) | 1 (6) | 1 (6) |
| Sinusitis NOS | 3 (7) | 10 (9) | 2 (<1) | 16 (6) | 2 (6) | 3 (8) | 2 (13) | 2 (13) |
| Influenza | 3 (3) | 3 (3) | 2 (<1) | 9 (4) | 0 | 1 (3) | 1 (6) | 1 (6) |
| Urinary tract infection NOS | 7 (6) | 8 (7) | 1 (<1) | 2 (<1) | 0 | 1 (3) | 2 (13) | 2 (13) |
| Bronchitis NOS | 0 | 2 (2) | 5 (2) | 10 (5) | 1 (3) | 3 (8) | 0 | 0 |
| Gastroenteritis viral NOS | 4 (3) | 4 (3) | 2 (<1) | 8 (4) | 0 | 1 (3) | 0 | 0 |
| Pneumonia NOS | 6 (5) | 6 (5) | 4 (2) | 4 (2) | 0 | 0 | 0 | 0 |
| Herpes simplex | 2 (2) | 2 (2) | 0 | 2 (<1) | 0 | 0 | 0 | 0 |
| Respiratory tract infection NOS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GASTROINTESTINAL DISORDERS | | | | | | | | |
| Nausea | 30 (26) | 33 (29) | 20 (10) | 41 (20) | 5 (14) | 9 (25) | 4 (25) | 4 (25) |
| Vomiting NOS | 11 (10) | 13 (11) | 7 (3) | 11 (5) | 0 | 0 | 2 (13) | 2 (13) |
| Diarrhoea NOS | 2 (2) | 4 (3) | 2 (<1) | 6 (3) | 0 | 1 (3) | 0 | 0 |
| Toothache | 4 (3) | 5 (4) | 2 (<1) | 4 (2) | 0 | 3 (8) | 0 | 0 |
| Dyspepsia | 2 (2) | 3 (3) | 3 (1) | 10 (5) | 1 (3) | 1 (3) | 0 | 0 |
| Abdominal pain NOS | 2 (2) | 3 (3) | 2 (<1) | 4 (2) | 2 (6) | 2 (6) | 0 | 0 |
| Abdominal pain upper | 3 (3) | 3 (3) | 1 (<1) | 2 (<1) | 1 (3) | 1 (3) | 0 | 0 |
| Gastritis alcoholic | 3 (3) | 3 (3) | 1 (<1) | 1 (<1) | 0 | 0 | 0 | 0 |
| Erection | 0 | 0 | 0 | 1 (<1) | 1 (3) | 1 (3) | 1 (6) | 1 (6) |
| Oesophageal ulcer haemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 1 (6) | 1 (6) |
| PSYCHIATRIC DISORDERS | | | | | | | | |
| Depression | 16 (14) | 21 (18) | 17 (8) | 45 (22) | 4 (11) | 8 (22) | 0 | 0 |
| Insomnia | 3 (3) | 6 (5) | 6 (3) | 18 (9) | 1 (3) | 3 (8) | 0 | 0 |
| Anxiety NEC | 8 (7) | 10 (9) | 3 (2) | 8 (4) | 1 (3) | 1 (3) | 0 | 0 |
| Alcoholism | 4 (3) | 4 (3) | 4 (2) | 12 (6) | 1 (3) | 3 (8) | 0 | 0 |
| Drug dependence | 2 (2) | 2 (2) | 0 | 3 (1) | 0 | 2 (6) | 0 | 0 |
| | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 2 (6) | 0 | 0 |

(table continues on next page)

(Source: Applicant's Summary of Clinical Safety, Table 2.6, p. 27-32)

Appendix 2: Most common AEs after 6 months (all data compared with NDA) (continued)

Vivitrol (ALK201-003EXT and ALK201-010)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | All Subjects | | Placebo to 180mg | | 180mg to 180mg | | Placebo to 360mg | |
|---|--------------|----------|------------------|---------|----------------|---------|------------------|---------|
| | NDA* | Update* | NDA* | Update* | NDA* | Update* | NDA* | Update* |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 94 (16) | 139 (23) | 11 (20) | 12 (22) | 31 (30) | 32 (31) | 19 (32) | 21 (35) |
| Arthralgia | 23 (4) | 43 (7) | 2 (4) | 4 (7) | 8 (8) | 11 (11) | 2 (3) | 5 (5) |
| Back pain | 31 (5) | 43 (7) | 3 (9) | 6 (11) | 5 (5) | 5 (5) | 6 (10) | 6 (10) |
| Pain in limb | 17 (3) | 24 (4) | 1 (2) | 1 (2) | 5 (5) | 5 (5) | 5 (5) | 7 (12) |
| Bursitis | 0 | 2 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Aseptic necrosis bone | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Intervertebral disc herniation | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 104 (18) | 126 (22) | 16 (29) | 20 (36) | 29 (28) | 30 (29) | 26 (43) | 27 (45) |
| Fatigue | 30 (5) | 39 (7) | 5 (9) | 7 (13) | 5 (5) | 7 (7) | 9 (15) | 9 (15) |
| Injection site pain | 20 (3) | 24 (4) | 6 (11) | 6 (11) | 2 (2) | 2 (2) | 4 (7) | 5 (3) |
| Influenza like illness | 17 (3) | 20 (3) | 4 (7) | 4 (7) | 5 (9) | 11 (11) | 2 (3) | 2 (3) |
| Injection site induration | 18 (3) | 20 (3) | 4 (7) | 4 (7) | 1 (<1) | 1 (<1) | 9 (15) | 10 (17) |
| Fall | 5 (<1) | 9 (2) | 2 (4) | 3 (5) | 0 | 1 (<1) | 0 | 1 (2) |
| NERVOUS SYSTEM DISORDERS | 88 (15) | 120 (21) | 12 (22) | 12 (22) | 22 (22) | 27 (26) | 12 (20) | 19 (22) |
| Headache NOS | 49 (9) | 66 (11) | 4 (7) | 4 (7) | 16 (16) | 19 (19) | 8 (13) | 8 (13) |
| Dizziness | 14 (2) | 19 (3) | 4 (7) | 4 (7) | 3 (3) | 3 (3) | 1 (2) | 1 (2) |
| Sinus headache | 4 (<1) | 7 (1) | 0 | 0 | 0 | 0 | 1 (2) | 1 (2) |
| Mental impairment NOS | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 85 (15) | 112 (20) | 13 (24) | 14 (25) | 15 (15) | 17 (17) | 14 (23) | 14 (23) |
| Laceration | 6 (1) | 13 (2) | 1 (2) | 1 (2) | 1 (<1) | 1 (<1) | 2 (3) | 2 (3) |
| Joint sprain | 10 (2) | 12 (2) | 1 (2) | 1 (2) | 4 (4) | 5 (5) | 2 (3) | 2 (3) |
| Back injury NOS | 8 (1) | 11 (2) | 3 (5) | 3 (5) | 0 | 1 (<1) | 1 (2) | 1 (2) |
| Muscle strain | 6 (1) | 7 (1) | 2 (4) | 2 (4) | 0 | 0 | 3 (5) | 3 (5) |
| Post procedural pain | 2 (<1) | 5 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Animal bite | 1 (<1) | 4 (<1) | 0 | 1 (2) | 0 | 0 | 1 (2) | 1 (2) |

(Table continues on next page)

(Source: Applicant's Summary of Clinical Safety, Table 2.6, p. 27-32)

Appendix 2: Most common AEs after 6 months (all data compared with NDA) (continued)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | Vivitrol 380mg to 380mg (ALK21-006 and ALK21-010) | | Vivitrol 380mg (ALK21-006 and ALK21-006Ext) | | Oral Malteneone (ALK21-006) | | Oral to 380mg ALK21-006Ext | |
|---|---|---------|---|---------|--------------------------------|----------|----------------------------------|---------|
| | NDA* | Update* | NDA* | Update* | NDA* | Update** | NDA* | Update* |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 25 (22) | 28 (24) | 5 (2) | 31 (15) | 3 (8) | 7 (11) | 3 (19) | |
| Arthralgia | 9 (8) | 11 (10) | 1 (<1) | 9 (4) | 1 (3) | 3 (8) | 1 (6) | |
| Back pain | 11 (10) | 12 (10) | 2 (<1) | 9 (4) | 2 (6) | 5 (14) | 0 | |
| Pain in limb | 5 (4) | 6 (5) | 1 (<1) | 5 (2) | 0 | 0 | 0 | |
| Bursitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (6) | |
| Aseptic necrosis bone | 0 | 0 | 0 | 0 | 0 | 1 (3) | 1 (6) | |
| Intervertebral disc herniation | 0 | 0 | 0 | 0 | 0 | 0 | 1 (6) | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 21 (19) | 23 (20) | 11 (5) | 23 (11) | 1 (3) | 3 (8) | 0 | |
| Fatigue | 6 (7) | 8 (7) | 2 (<1) | 7 (3) | 1 (3) | 1 (3) | 0 | |
| Injection site pain | 6 (5) | 6 (5) | 2 (<1) | 5 (2) | 0 | 0 | 0 | |
| Influenza like illness | 1 (<1) | 1 (<1) | 1 (<1) | 2 (<1) | 0 | 0 | 0 | |
| Injection site induration | 2 (2) | 2 (2) | 2 (<1) | 3 (1) | 0 | 0 | 0 | |
| Fall | 3 (3) | 4 (3) | 0 | 0 | 0 | 0 | 0 | |
| NERVOUS SYSTEM DISORDERS | 25 (22) | 27 (23) | 16 (8) | 36 (17) | 1 (3) | 3 (8) | 2 (13) | |
| Headache NOS | 10 (9) | 13 (11) | 11 (5) | 21 (10) | 0 | 1 (3) | 0 | |
| Dizziness | 3 (3) | 6 (5) | 3 (1) | 4 (2) | 0 | 0 | 1 (6) | |
| Sinus headache | 2 (2) | 3 (3) | 0 | 1 (<1) | 1 (3) | 2 (6) | 0 | |
| Mental impairment NOS | 0 | 0 | 0 | 0 | 0 | 0 | 1 (6) | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 20 (17) | 23 (20) | 20 (10) | 36 (17) | 3 (8) | 8 (22) | 2 (13) | |
| Laceration | 2 (2) | 2 (2) | 0 | 4 (2) | 0 | 3 (8) | 0 | |
| Joint sprain | 1 (<1) | 1 (<1) | 2 (<1) | 3 (1) | 0 | 0 | 0 | |
| Back injury NOS | 1 (<1) | 1 (<1) | 1 (<1) | 2 (<1) | 2 (6) | 3 (8) | 0 | |
| Muscle strain | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | |
| Post procedural pain | 2 (2) | 2 (2) | 0 | 1 (<1) | 0 | 0 | 1 (6) | |
| Animal bite | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 1 (6) | |

(Table continues on next page)

(Source: Applicant's Summary of Clinical Safety, Table 2.6, p. 27-32)

Appendix 2: Most common AEs after 6 months (all data compared with NDA) (continued)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | All Subjects | | Placebo to 180mg | | 180mg to 180mg | | Placebo to 360mg | |
|--|-------------------|-------------------|------------------|-----------------|------------------|------------------|------------------|-----------------|
| | NDA* | Update* | NDA* | Update* | NDA* | Update* | NDA* | Update* |
| INVESTIGATIONS | | | | | | | | |
| Blood creatine phosphokinase increased | 55 (10) 11 (2) | 92 (16) 17 (3) | 6 (15) 0 | 9 (16) 0 | 9 (5) 0 | 14 (14) 0 | 5 (10) 2 (3) | 8 (13) 2 (3) |
| Weight decreased | 2 (<1) | 3 (1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Weight increased | 2 (<1) | 4 (<1) | 0 | 1 (2) | 0 | 0 | 0 | 0 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | | | | | | |
| Rash NOS | 57 (10) 11 (2) | 78 (14) 20 (3) | 4 (7) 1 (2) | 4 (7) 2 (5) | 17 (17) 3 (3) | 22 (22) 3 (3) | 9 (15) 3 (5) | 9 (15) 3 (5) |
| RESPIRATORY, THORACIC AND MEDISTINAL DISORDERS | | | | | | | | |
| Pharyngolaryngeal pain | 10 (2) | 16 (3) | 2 (4) | 2 (4) | 3 (3) | 6 (6) | 0 | 0 |
| Nasal congestion | 5 (2) | 13 (2) | 0 | 0 | 3 (3) | 3 (3) | 3 (3) | 3 (5) |
| METABOLISM AND NUTRITION DISORDERS | | | | | | | | |
| Appetite decreased NOS | 25 (4) 9 (2) | 45 (8) 13 (2) | 6 (11) 4 (7) | 7 (13) 5 (9) | 4 (4) 0 | 6 (6) 0 | 4 (7) 2 (3) | 7 (12) 3 (5) |
| Appetite increased NOS | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | | | | | | | |
| Menstruation irregular | 16 (3) 0 | 28 (5) 3 (<1) | 2 (4) 0 | 2 (4) 0 | 4 (4) 0 | 5 (5) 0 | 2 (3) 0 | 3 (5) 1 (2) |
| VASCULAR DISORDERS | | | | | | | | |
| Hypertension NOS | 15 (3) 9 (2) | 26 (5) 17 (3) | 3 (5) 1 (2) | 4 (7) 2 (4) | 6 (6) 4 (4) | 8 (8) 6 (6) | 2 (3) 1 (2) | 3 (5) 1 (2) |
| IMMUNE SYSTEM DISORDERS | | | | | | | | |
| Seasonal allergy | 18 (3) 6 (1) | 21 (4) 11 (2) | 5 (9) 3 (5) | 5 (9) 3 (5) | 4 (4) 2 (2) | 4 (4) 2 (2) | 1 (2) 1 (2) | 3 (5) 3 (5) |

(Table continues on next page)

(Source: Applicant's Summary of Clinical Safety, Table 2.6, p. 27-32)

Appendix 2: Most common AEs after 6 months (all data compared with NDA) (continued)

| System Organ Class (MedDRA) Preferred Term (MedDRA) | Vivitrol 360mg to 360mg (ALK21-006Ext and ALK21-019) | | Vivitrol 360mg (ALK21-006 and ALK21-006Ext) | | Oral Naltrexone (ALK21-006) | | Oral to 360mg ALK21-006Ext Update* | |
|--|--|---------|---|---------|--------------------------------|---------|---|---------|
| | NDA* | Update* | NDA* | Update* | NDA* | Update* | NDA* | Update* |
| INVESTIGATIONS | 15 (13) | 15 (13) | 14 (7) | 39 (19) | 3 (9) | 5 (14) | 2 (13) | |
| Blood creatine phosphokinase increased | 4 (3) | 4 (3) | 4 (2) | 10 (5) | 1 (3) | 1 (3) | 0 | |
| Weight decreased | 1 (<1) | 1 (<1) | 1 (<1) | 6 (3) | 0 | 0 | 1 (6) | |
| Weight increased | 1 (<1) | 1 (<1) | 0 | 0 | 1 (3) | 1 (3) | 1 (6) | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 14 (12) | 19 (17) | 13 (6) | 24 (12) | 0 | 0 | 0 | |
| Rash NOS | 1 (<1) | 4 (3) | 3 (1) | 8 (4) | 0 | 0 | 0 | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 14 (12) | 16 (14) | 4 (2) | 23 (11) | 2 (6) | 4 (11) | 0 | |
| Pharyngolaryngeal pain | 5 (4) | 5 (4) | 0 | 3 (1) | 0 | 0 | 0 | |
| Nasal congestion | 2 (2) | 3 (3) | 1 (<1) | 3 (1) | 0 | 1 (3) | 0 | |
| METABOLISM AND NUTRITION DISORDERS | 8 (7) | 9 (8) | 2 (<1) | 14 (7) | 1 (3) | 1 (3) | 1 (6) | |
| Appetite decreased NOS | 2 (2) | 2 (2) | 1 (<1) | 3 (1) | 0 | 0 | 0 | |
| Appetite increased NOS | 0 | 0 | 0 | 0 | 0 | 0 | 1 (6) | |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 7 (6) | 7 (6) | 3 (1) | 9 (4) | 0 | 1 (3) | 1 (6) | |
| Menstruation irregular | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 1 (6) | |
| VASCULAR DISORDERS | 1 (<1) | 3 (3) | 2 (<1) | 7 (3) | 1 (3) | 1 (3) | 0 | |
| Hypertension NOS | 0 | 1 (<1) | 2 (<1) | 6 (3) | 1 (3) | 1 (3) | 0 | |
| IMMUNE SYSTEM DISORDERS | 6 (5) | 6 (5) | 2 (<1) | 3 (1) | 0 | 0 | 0 | |
| Seasonal allergy | 0 | 1 (<1) | 0 | 2 (<1) | 0 | 0 | 0 | |

* 'NDA' columns provide counts as reported with the original NDA, 'Update' columns are with data as of 6/31/2005.

† Subjects who were dosed in ALK21-006Ext are counted only once for the All Subject column at each row.

‡ Events with onset prior to first Vivitrol dose of ALK21-006Ext (if enrolled).

§ Events with onset after first Vivitrol dose of ALK21-006Ext.

Note: Percentages are out of number of subjects dosed after 6 months.

(Source: Applicant's Summary of Clinical Safety, Table 2.6, p. 27-32)

10.3 Appendix 3: Discontinuations due to AEs

Number (%) of Subjects Reporting Adverse Events Resulting in Treatment/Study Discontinuation after 6 Months in Studies in Dependent Subjects

| System Organ Class (MedDRA) Preferred Term (MedDRA) | Vivitrol | | | | | | | | | | | |
|---|----------------------------|----------|-----------------|----------|-----------------|----------|-----------------|----------|-----------------|----------|-----------------|----------|
| | Vivitrol | | | | | Vivitrol | | | | | | |
| | ALK21-006EXT and ALK21-010 | | 360MG ALK21-006 | |
| | Placebo | 150mg | Placebo | 360mg |
| | Subjects | to 150mg | to 150mg | to 360mg | to 360mg | to 360mg |
| No. of subjects dosed after 6 months | 574 | 55 | 102 | 60 | 115 | 206 | 36 | 16 | | | | |
| No. of subjects with an AE resulting in treatment/study discontinuation | 45 (8) | 3 (5) | 6 (6) | 11 (18) | 13 (11) | 10 (5) | 1 (3) | 1 (6) | | | | |
| GENERAL DISORDERS AND ADMINISTRATION | 11 (2) | 0 | 3 (3) | 5 (8) | 3 (3) | 0 | 0 | 0 | | | | |
| SITE COMBITIONS | | | | | | | | | | | | |
| Injection site induration | 4 (<1) | 0 | 0 | 4 (7) | 0 | 0 | 0 | 0 | | | | |
| Injection site pain | 3 (<1) | 0 | 0 | 3 (5) | 0 | 0 | 0 | 0 | | | | |
| Fatigue | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | | | | |
| Feeling jittery | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | | | | |
| Influenza like illness | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | | | | |
| Injection site anaesthesia | 1 (<1) | 0 | 0 | 1 (2) | 0 | 0 | 0 | 0 | | | | |
| Injection site urticaria | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 | 0 | | | | |
| PAIN NOS | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | | | | |
| Pyrexia | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 0 | | | | |
| PSYCHIATRIC DISORDERS | | | | | | | | | | | | |
| Alcoholism | 3 (1) | 1 (2) | 1 (<1) | 1 (2) | 2 (2) | 3 (1) | 0 | 0 | | | | |
| Agitation | 2 (<1) | 1 (2) | 0 | 0 | 0 | 1 (<1) | 0 | 0 | | | | |
| | 1 (<1) | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 0 | | | | |

SOURCE: J:\BDM\VALIEXXONE\INDRUP12\PROG\TABLES\DEV\RES_AETRDISCONTMONTH.SAS

* Subjects who were dosed in ALK21-006EXT are counted only once for the All Subject column at each row.

* Events with onset prior to first Vivitrol dose of ALK21-006EXT (if enrolled).

* Events with onset after first Vivitrol dose of ALK21-006EXT.

Note: Percentages are out of number of subjects dosed after 6 months.

(Source: Applicant's Summary of Clinical Safety, Table 14.2, P. 238-41)

Appendix 3: Discontinuations due to AEs (continued)

Number (%) of Subjects Reporting Adverse Events Resulting in Treatment/Study Discontinuation after 6 Months in Studies in Dependent Subjects

| System Organ Class (MedDRA) Preferred Term (MedDRA) | Vivitrol | | | | | | Vivitrol Oral to 380mg, ALK21-006 EXT |
|--|--|---------------------|-------------------|-------------------------------|--|---|---|
| | ALK21-006EXT and ALK21-010 | | | | | | |
| | Placebo Subjects: to 190mg to 380mg | Placebo to 380mg | 380mg to 380mg | 380mg and ALK21- 006EXT | Oral ALK21-006 Naltrexone, ALK21-006 EXT | Oral Naltrexone, ALK21-006 EXT | |
| Completed suicide | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Depression | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Emotional disturbance NOS | 1 (<1) | 0 | 0 | 1 (2) | 0 | 0 | 0 |
| Insomnia | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Suicide attempt | 1 (<1) | 0 | 0 | 0 | 0 | 1 (<1) | 0 |
| GASTROINTESTINAL DISORDERS | | | | | | | |
| Nausea | 7 (1) | 1 (2) | 0 | 2 (3) | 3 (3) | 0 | 1 (6) |
| Abdominal pain upper | 5 (<1) | 1 (2) | 0 | 1 (2) | 2 (2) | 0 | 1 (6) |
| Gastritis NOS | 1 (<1) | 0 | 0 | 1 (2) | 0 | 0 | 0 |
| INVESTIGATIONS | | | | | | | |
| Liver function tests NOS abnormal | 4 (<1) | 0 | 0 | 0 | 2 (2) | 2 (<1) | 0 |
| Blood creatine phosphokinase increased | 3 (<1) | 0 | 0 | 0 | 1 (<1) | 2 (<1) | 0 |
| NERVOUS SYSTEM DISORDERS | | | | | | | |
| Headache NOS | 4 (<1) | 0 | 0 | 1 (2) | 0 | 2 (<1) | 0 |
| Memory impairment | 2 (<1) | 0 | 0 | 1 (2) | 0 | 1 (<1) | 0 |
| Mental impairment NOS | 1 (<1) | 0 | 0 | 0 | 0 | 1 (<1) | 0 |
| | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 1 (6) |

SOURCE: J:\BRM\NALTREXONE\INDAPD22\PROG\TABLES\DEV\ISS_AETRIDISOGI6MORH.SAS
 * Subjects who were dosed in ALK21-006EXT are counted only once for the All Subject column at each row.
 * Events with onset prior to first Vivitrol dose of ALK21-006EXT (if enrolled).
 * Events with onset after first Vivitrol dose of ALK21-006EXT.
 Note: Percentages are out of number of subjects dosed after 6 months.

(Source: Applicant's Summary of Clinical Safety, Table 14.2, P. 238-41)

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Appendix 3: Discontinuations due to AEs (continued)

Number (%) of Subjects Reporting Adverse Events Resulting in Treatment/Study Discontinuation after 6 Months in Studies in Subjects in Dependent Subjects

| System Organ Class (MedDRA) Preferred Term (MedDRA) | Vivitrol | | | | | | Vivitrol Oral to 380mg, ALK21-006 Maltrekone, ALK21-006 Ext |
|---|----------------------------------|-------------------|---------------------|-------------------|-------------------------------|----------------------------------|---|
| | ALK21-006Ext and ALK21-010 | | | | | | |
| | Placebo Subjects: to 190mg | 190mg to 190mg | Placebo to 380mg | 380mg to 380mg | 380mg and ALK21- 006Ext | Oral Maltrekone, ALK21-006 | |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 3 (<1) | 0 | 2 (3) | 1 (<1) | 0 | 0 | |
| Intervertebral disc degeneration NOS | 1 (<1) | 0 | 1 (2) | 0 | 0 | 0 | |
| Myalgia | 1 (<1) | 0 | 1 (2) | 0 | 0 | 0 | |
| Pain in limb | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 3 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 0 | |
| Breast cancer NOS | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | |
| Pancreatic carcinoma NOS | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | |
| Prostate cancer NOS | 1 (<1) | 0 | 0 | 0 | 0 | 0 | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 2 (<1) | 0 | 2 (3) | 0 | 0 | 0 | |
| Eosinophilia | 2 (<1) | 0 | 2 (3) | 0 | 0 | 0 | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 2 (<1) | 0 | 0 | 0 | 1 (<1) | 1 (3) | |
| Overdose NOS | 1 (<1) | 0 | 0 | 0 | 0 | 1 (3) | |
| Postoperative fever | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 2 (<1) | 0 | 1 (<1) | 0 | 1 (<1) | 0 | |

SOURCE: J:\EDM\ALTRIXONE\HDAUFED12\PROG\TABLES\DEVAISS\ALTRIXONE\6MONTH\SAS

* Subjects who were dosed in ALK21-006Ext are counted only once for the All Subject column at each row.

* Events with onset prior to first Vivitrol dose of ALK21-006Ext (if enrolled).

* Events with onset after first Vivitrol dose of ALK21-006Ext.

Note: Percentages are out of number of subjects dosed after 6 months.

(Source: Applicant's Summary of Clinical Safety, Table 14.2, P. 238-41)

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Appendix 3: Discontinuations due to AEs (continued)

Number (%) of Subjects Reporting Adverse Events Resulting in Treatment/Study Discontinuation after 6 Months in Studies in Dependent Subjects

| System Organ Class (MedDRA) Preferred Term (MedDRA) | Vivitrol | | | | | | Vivitrol Oral to 380mg, ALK21-006 EXT |
|--|----------------------------------|-------------------|---------------------|-------------------|---|---|---|
| | ALK21-006EXT and ALK21-010 | | | | | | |
| | Placebo Subjects: to 190mg | 190mg to 190mg | Placebo to 380mg | 380mg to 380mg | Oral ALK21-006 and ALK21- 006EXT | Oral Maltrexone, ALK21-006 EXT | |
| Rash generalised | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Urticaria NOS | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| CARDIAC DISORDERS | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Cardiac failure congestive | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| HEPATOBIILIARY DISORDERS | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Hepatitis acute | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| INFECTIONS AND INFESTATIONS | 1 (<1) | 1 (2) | 0 | 0 | 0 | 0 | 0 |
| Methicillin-resistant staphylococcal aureus infection | 1 (<1) | 1 (2) | 0 | 0 | 0 | 0 | 0 |
| METABOLISM AND NUTRITION DISORDERS | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Appetite decreased NOS | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Pregnancy NOS | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 |

SOURCE: J:\BDM\NALIREXONE\INDUPTIC\PROG\TABLES\DEVISS_AETRIDISGIGNONTH.SAS

: Subjects who were dosed in ALK21-006EXT are counted only once for the All Subject column at each row.

: Events with onset prior to first Vivitrol dose of ALK21-006EXT (if enrolled).

: Events with onset after first Vivitrol dose of ALK21-006EXT.

Note: Percentages are out of number of subjects dosed after 6 months.

(Source: Applicant's Summary of Clinical Safety, Table 14.2, P. 238-41)

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10.4 Appendix 4: Subjects who shifted from normal CPK at baseline to high

Subjects Who Shifted from Normal Creatinine Phosphokinase (U/L) at Baseline to High/3x High

| Treatment | Study ID | Subject ID | Baseline Value | Peak Week | Peak Value | Multiple of Upper Limit |
|-----------|-----------|------------|----------------|-----------|------------|-------------------------|
| Placebo | ALK21-002 | 202-012 | 66 | Week 4 | 484 | 3.2 |
| | ALK21-003 | 202-003 | 94 | Week 16 | 212 | 1.1 |
| | ALK21-003 | 202-007 | 172 | Week 12 | 405 | 2.0 |
| | ALK21-003 | 202-014 | 135 | Week 20 | 247 | 1.2 |
| | ALK21-003 | 202-019 | 72 | Week 24 | 306 | 1.5 |
| | ALK21-003 | 208-005 | 160 | Week 8 | 418 | 2.1 |
| | ALK21-003 | 208-009 | 164 | Week 12 | 292 | 1.5 |
| | ALK21-003 | 208-021 | 141 | Week 12 | 206 | 1.0 |
| | ALK21-003 | 209-004 | 184 | Week 4 | 222 | 1.1 |
| | ALK21-003 | 209-028 | 97 | Week 8 | 2461 | 14.6 |
| | ALK21-003 | 209-038 | 118 | Week 4 | 172 | 1.0 |
| | ALK21-003 | 210-007 | 119 | Week 4 | 239 | 1.4 |
| | ALK21-003 | 210-021 | 198 | Week 4 | 544 | 2.7 |
| | ALK21-003 | 210-034 | 143 | Week 20 | 325 | 1.6 |
| | ALK21-003 | 211-016 | 139 | Week 12 | 213 | 1.3 |
| | ALK21-003 | 211-019 | 143 | Week 16 | 1116 | 5.6 |
| | ALK21-003 | 212-022 | 143 | Week 4 | 220 | 1.1 |
| | ALK21-003 | 213-005 | 94 | Week 4 | 431 | 2.2 |
| | ALK21-003 | 214-001 | 162 | Week 4 | 257 | 1.3 |
| | ALK21-003 | 214-012 | 75 | Week 24 | 226 | 1.1 |
| | ALK21-003 | 214-034 | 128 | Week 12 | 264 | 1.3 |
| | ALK21-003 | 215-001 | 66 | Week 16 | 417 | 2.1 |
| | ALK21-003 | 215-008 | 81 | Week 24 | 343 | 1.7 |
| | ALK21-003 | 215-023 | 115 | Week 20 | 528 | 2.7 |
| | ALK21-003 | 216-004 | 161 | Week 4 | 322 | 1.6 |
| | ALK21-003 | 216-015 | 63 | Week 8 | 346 | 1.7 |
| | ALK21-003 | 216-017 | 50 | Week 20 | 459 | 2.3 |
| | ALK21-003 | 217-002 | 45 | Week 16 | 1125 | 6.7 |
| | ALK21-003 | 217-015 | 154 | Week 12 | 267 | 1.3 |
| | ALK21-003 | 217-017 | 188 | Week 16 | 233 | 1.2 |
| | ALK21-003 | 217-020 | 79 | Week 16 | 256 | 1.3 |
| | ALK21-003 | 218-007 | 131 | Week 12 | 279 | 1.4 |

Appendix 4: Subjects who shifted from normal CPK at baseline to high at study end (continued)

Subjects Who Shifted from Normal Creatinine Phosphokinase (U/L) at Baseline to High/3x High

| Treatment | Study ID | Subject ID | Baseline Value | Peak Week | Peak Value | Multiple of Upper Limit | |
|-----------|-----------|------------|----------------|-----------|------------|-------------------------|-----|
| Placebo | ALK21-003 | 219-006 | 152 | Week 4 | 184 | 1.1 | |
| | ALK21-003 | 221-004 | 129 | Week 8 | 224 | 1.1 | |
| | ALK21-003 | 221-007 | 143 | Week 4 | 300 | 1.8 | |
| | ALK21-003 | 221-011 | 74 | Week 4 | 2321 | 13.7 | |
| | ALK21-003 | 224-017 | 73 | Week 24 | 540 | 3.2 | |
| | ALK21-003 | 224-023 | 187 | Week 16 | 274 | 1.4 | |
| | ALK21-003 | 225-034 | 101 | Week 16 | 170 | 1.0 | |
| | ALK21-003 | 226-005 | 78 | Week 24 | 216 | 1.1 | |
| | ALK21-003 | 229-003 | 107 | Week 24 | 189 | 1.1 | |
| | Oral 50mg | ALK21-006 | 214-009 | 99 | Week 16 | 236 | 1.4 |
| | | ALK21-006 | 231-015 | 46 | Week 12 | 185 | 1.1 |
| | | ALK21-006 | 234-008 | 127 | Week 24 | 347 | 1.8 |
| ALK21-006 | | 235-005 | 165 | Week 12 | 717 | 3.6 | |
| ALK21-006 | | 236-010 | 133 | Week 8 | 272 | 1.4 | |
| ALK21-006 | | 238-006 | 103 | Week 20 | 838 | 4.2 | |
| ALK21-006 | | 239-008 | 135 | Week 24 | 201 | 1.2 | |
| ALK21-006 | | 239-019 | 157 | Week 24 | 295 | 1.5 | |
| ALK21-006 | | 240-003 | 144 | Week 24 | 207 | 1.0 | |
| ALK21-006 | | 242-002 | 99 | Week 4 | 232 | 1.2 | |
| ALK21-006 | | 245-021 | 151 | Week 4 | 223 | 1.1 | |
| ALK21-006 | | 246-004 | 161 | Week 4 | 253 | 1.3 | |
| ALK21-006 | | 248-011 | 175 | Week 4 | 498 | 2.5 | |
| ALK21-006 | | 254-007 | 124 | Week 12 | 396 | 2.0 | |
| ALK21-006 | | 255-001 | 127 | Week 16 | 214 | 1.1 | |
| 400mg | | ALK21-002 | 003-003 | 101 | Week 4 | 265 | 1.8 |
| | | ALK21-002 | 004-003 | 50 | Week 8 | 265 | 1.8 |
| | | ALK21-002 | 202-007 | 117 | Week 16 | 163 | 1.1 |
| | ALK21-002 | 202-008 | 140 | Week 16 | 202 | 1.3 | |
| | ALK21-002 | 202-018 | 125 | Week 4 | 475 | 3.2 | |
| | ALK21-002 | 202-023 | 150 | Week 12 | 245 | 1.6 | |

Appendix 4: Subjects who shifted from normal CPK at baseline to high at study end (continued)

| Subjects Who Shifted from Normal Creatinine Phosphokinase (U/L) at Baseline to High/3x High | | | | | | |
|---|-----------|------------|----------------|-----------|------------|-------------------------|
| Treatment | Study ID | Subject ID | Baseline Value | Peak Week | Peak Value | Multiple Of Upper Limit |
| 400mg | ALK21-002 | 202-025 | 103 | Week 4 | 430 | 2.9 |
| | ALK21-002 | 206-003 | 94 | Week 16 | 285 | 1.9 |
| 380mg | ALK21-003 | 202-017 | 127 | Week 12 | 522 | 3.1 |
| | ALK21-003 | 208-003 | 112 | Week 8 | 261 | 1.3 |
| | ALK21-003 | 208-004 | 136 | Week 20 | 214 | 1.3 |
| | ALK21-003 | 208-011 | 88 | Week 4 | 223 | 1.3 |
| | ALK21-003 | 208-016 | 189 | Week 20 | 394 | 2.0 |
| | ALK21-003 | 208-019 | 196 | Week 24 | 288 | 1.5 |
| | ALK21-003 | 209-011 | 109 | Week 24 | 283 | 1.4 |
| | ALK21-003 | 209-033 | 95 | Week 20 | 257 | 1.3 |
| | ALK21-003 | 209-037 | 136 | Week 16 | 220 | 1.1 |
| | ALK21-003 | 210-015 | 152 | Week 20 | 312 | 1.6 |
| | ALK21-003 | 210-030 | 168 | Week 4 | 341 | 1.7 |
| | ALK21-003 | 210-032 | 133 | Week 8 | 232 | 1.2 |
| | ALK21-003 | 211-023 | 195 | Week 12 | 381 | 1.9 |
| | ALK21-003 | 212-007 | 176 | Week 4 | 226 | 1.1 |
| | ALK21-003 | 212-011 | 105 | Week 4 | 209 | 1.1 |
| | ALK21-003 | 212-023 | 80 | Week 4 | 980 | 4.9 |
| | ALK21-003 | 213-002 | 84 | Week 20 | 255 | 1.5 |
| | ALK21-003 | 213-013 | 93 | Week 4 | 365 | 1.8 |
| | ALK21-003 | 214-003 | 171 | Week 4 | 229 | 1.2 |
| | ALK21-003 | 214-026 | 122 | Week 4 | 244 | 1.2 |
| | ALK21-003 | 214-029 | 109 | Week 16 | 215 | 1.1 |
| | ALK21-003 | 214-036 | 166 | Week 20 | 198 | 1.2 |
| | ALK21-003 | 214-039 | 192 | Week 16 | 475 | 2.4 |
| | ALK21-003 | 216-021 | 65 | Week 8 | 206 | 1.0 |
| | ALK21-003 | 216-025 | 124 | Week 24 | 222 | 1.1 |
| | ALK21-003 | 217-014 | 86 | Week 4 | 349 | 1.8 |
| ALK21-003 | 217-021 | 85 | Week 20 | 855 | 5.1 | |
| ALK21-003 | 217-033 | 28 | Week 24 | 281 | 1.7 | |
| ALK21-003 | 217-045 | 56 | Week 8 | 237 | 1.2 | |

Appendix 4: Subjects who shifted from normal CPK at baseline to high at study end (continued)

| Subjects Who Shifted from Normal Creatinine Phosphokinase (U/L) at Baseline to High/3x High | | | | | | |
|---|-----------|------------|----------------|-----------|------------|-------------------------|
| Treatment | Study ID | Subject ID | Baseline Value | Peak Week | Peak Value | Multiple of Upper Limit |
| 380mg | ALK21-003 | 217-046 | 33 | Week 20 | 195 | 1.2 |
| | ALK21-003 | 218-012 | 80 | Week 24 | 217 | 1.1 |
| | ALK21-003 | 218-013 | 112 | Week 8 | 224 | 1.1 |
| | ALK21-003 | 218-019 | 90 | Week 8 | 543 | 2.7 |
| | ALK21-003 | 218-027 | 130 | Week 12 | 467 | 2.8 |
| | ALK21-003 | 220-013 | 116 | Week 4 | 297 | 1.5 |
| | ALK21-003 | 224-002 | 127 | Week 4 | 354 | 2.1 |
| | ALK21-003 | 224-008 | 97 | Week 4 | 254 | 1.5 |
| | ALK21-003 | 224-025 | 160 | Week 20 | 374 | 1.9 |
| | ALK21-003 | 224-027 | 187 | Week 8 | 324 | 1.6 |
| | ALK21-003 | 225-013 | 64 | Week 4 | 391 | 2.0 |
| | ALK21-003 | 225-026 | 109 | Week 24 | 209 | 1.1 |
| | ALK21-003 | 225-030 | 78 | Week 20 | 1302 | 6.6 |
| | ALK21-003 | 225-037 | 164 | Week 12 | 250 | 1.3 |
| | ALK21-003 | 225-040 | 125 | Week 16 | 252 | 1.5 |
| | ALK21-003 | 227-004 | 147 | Week 8 | 231 | 1.4 |
| | ALK21-003 | 227-011 | 81 | Week 4 | 237 | 1.2 |
| | ALK21-003 | 229-011 | 174 | Week 8 | 470 | 2.4 |
| | ALK21-003 | 230-002 | 79 | Week 20 | 217 | 1.1 |
| | ALK21-003 | 230-010 | 72 | Week 24 | 219 | 1.1 |
| | ALK21-006 | 214-001 | 129 | Week 4 | 278 | 1.4 |
| | ALK21-006 | 214-004 | 145 | Week 20 | 342 | 1.7 |
| | ALK21-006 | 214-007 | 86 | Week 16 | 173 | 1.0 |
| | ALK21-006 | 214-012 | 59 | Week 20 | 209 | 1.1 |
| | ALK21-006 | 214-013 | 132 | Week 16 | 268 | 1.6 |
| | ALK21-006 | 231-003 | 67 | Week 20 | 188 | 1.1 |
| | ALK21-006 | 231-004 | 182 | Week 20 | 729 | 3.7 |
| | ALK21-006 | 231-005 | 148 | Week 12 | 295 | 1.5 |
| | ALK21-006 | 231-007 | 100 | Week 24 | 187 | 1.1 |
| | ALK21-006 | 231-008 | 101 | Week 4 | 352 | 1.8 |
| | ALK21-006 | 231-009 | 102 | Week 20 | 347 | 1.8 |
| | ALK21-006 | 231-013 | 71 | Week 12 | 219 | 1.3 |

Appendix 4: Subjects who shifted from normal CPK at baseline to high at study end (continued)

| Subjects who Shifted from Normal Creatinine Phosphokinase (U/L) at Baseline to High/3x High | | | | | | |
|---|-----------|------------|----------------|-----------|------------|-------------------------|
| Treatment | Study ID | Subject ID | Baseline Value | Peak Week | Peak Value | Multiple of Upper Limit |
| 380mg | ALK21-006 | 231-017 | 94 | Week 24 | 289 | 1.7 |
| | ALK21-006 | 231-018 | 112 | Week 20 | 1913 | 9.7 |
| | ALK21-006 | 232-005 | 126 | Week 16 | 532 | 2.7 |
| | ALK21-006 | 232-014 | 99 | Week 20 | 214 | 1.1 |
| | ALK21-006 | 233-003 | 69 | Week 4 | 228 | 1.2 |
| | ALK21-006 | 233-005 | 64 | Week 4 | 201 | 1.2 |
| | ALK21-006 | 233-006 | 106 | Week 4 | 211 | 1.2 |
| | ALK21-006 | 233-012 | 82 | Week 4 | 231 | 1.2 |
| | ALK21-006 | 234-004 | 109 | Week 20 | 276 | 1.4 |
| | ALK21-006 | 234-005 | 196 | Week 8 | 224 | 1.1 |
| | ALK21-006 | 234-006 | 61 | Week 12 | 207 | 1.0 |
| | ALK21-006 | 235-001 | 133 | Week 24 | 543 | 2.7 |
| | ALK21-006 | 235-010 | 162 | Week 12 | 415 | 2.1 |
| | ALK21-006 | 235-014 | 84 | Week 12 | 722 | 3.6 |
| | ALK21-006 | 235-015 | 86 | Week 12 | 211 | 1.1 |
| | ALK21-006 | 235-018 | 64 | Week 8 | 388 | 2.3 |
| | ALK21-006 | 235-019 | 158 | Week 8 | 334 | 1.7 |
| | ALK21-006 | 236-007 | 124 | Week 16 | 392 | 2.0 |
| | ALK21-006 | 236-009 | 176 | Week 4 | 241 | 1.2 |
| | ALK21-006 | 236-016 | 135 | Week 24 | 545 | 2.8 |
| | ALK21-006 | 237-002 | 167 | Week 4 | 376 | 1.9 |
| | ALK21-006 | 237-007 | 117 | Week 4 | 316 | 1.6 |
| | ALK21-006 | 237-013 | 56 | Week 12 | 198 | 1.2 |
| | ALK21-006 | 237-028 | 152 | Week 4 | 202 | 1.0 |
| | ALK21-006 | 238-004 | 44 | Week 8 | 227 | 1.1 |
| | ALK21-006 | 238-009 | 105 | Week 20 | 276 | 1.4 |
| | ALK21-006 | 238-011 | 126 | Week 16 | 5897 | 34.9 |
| | ALK21-006 | 238-014 | 73 | Week 24 | 196 | 1.2 |
| | ALK21-006 | 238-017 | 143 | Week 4 | 400 | 2.0 |
| | ALK21-006 | 238-020 | 134 | Week 4 | 255 | 1.3 |
| ALK21-006 | 239-002 | 163 | Week 8 | 4444 | 22.4 | |
| ALK21-006 | 239-009 | 133 | Week 16 | 263 | 1.3 | |

Appendix 4: Subjects who shifted from normal CPK at baseline to high at study end (continued)

Subjects Who Shifted from Normal Creatinine Phosphokinase (U/L) at Baseline to High/3x High

| Treatment | Study ID | Subject ID | Baseline Value | Peak Week | Peak Value | Multiple of Upper Limit |
|-----------|-----------|------------|----------------|-----------|------------|-------------------------|
| 380mg | ALK21-006 | 239-017 | 127 | Week 12 | 244 | 1.2 |
| | ALK21-006 | 241-002 | 116 | Week 12 | 307 | 1.6 |
| | ALK21-006 | 241-005 | 57 | Week 8 | 742 | 3.7 |
| | ALK21-006 | 241-010 | 131 | Week 4 | 200 | 1.0 |
| | ALK21-006 | 241-011 | 86 | Week 24 | 179 | 1.1 |
| | ALK21-006 | 241-016 | 154 | Week 4 | 205 | 1.0 |
| | ALK21-006 | 245-017 | 105 | Week 8 | 217 | 1.3 |
| | ALK21-006 | 245-020 | 112 | Week 24 | 283 | 1.4 |
| | ALK21-006 | 245-025 | 86 | Week 20 | 261 | 1.5 |
| | ALK21-006 | 245-026 | 73 | Week 4 | 259 | 1.3 |
| | ALK21-006 | 245-029 | 47 | Week 16 | 170 | 1.0 |
| | ALK21-006 | 245-030 | 160 | Week 8 | 272 | 1.4 |
| | ALK21-006 | 245-038 | 112 | Week 12 | 2002 | 11.8 |
| | ALK21-006 | 245-040 | 151 | Week 4 | 238 | 1.2 |
| | ALK21-006 | 246-003 | 85 | Week 8 | 391 | 2.0 |
| | ALK21-006 | 246-009 | 84 | Week 20 | 234 | 1.4 |
| | ALK21-006 | 246-011 | 108 | Week 8 | 204 | 1.0 |
| | ALK21-006 | 246-015 | 138 | Week 16 | 673 | 3.4 |
| | ALK21-006 | 246-017 | 141 | Week 8 | 235 | 1.2 |
| | ALK21-006 | 246-024 | 176 | Week 12 | 237 | 1.2 |
| | ALK21-006 | 247-004 | 103 | Week 12 | 322 | 1.6 |
| | ALK21-006 | 247-005 | 115 | Week 16 | 293 | 1.5 |
| | ALK21-006 | 248-003 | 132 | Week 16 | 308 | 1.8 |
| | ALK21-006 | 248-013 | 111 | Week 8 | 334 | 1.7 |
| | ALK21-006 | 250-003 | 80 | Week 4 | 178 | 1.1 |
| | ALK21-006 | 250-020 | 152 | Week 12 | 5169 | 26.1 |
| | ALK21-006 | 250-029 | 169 | Week 8 | 471 | 2.4 |
| | ALK21-006 | 251-001 | 107 | Week 24 | 272 | 1.4 |
| | ALK21-006 | 251-003 | 95 | Week 4 | 223 | 1.3 |
| | ALK21-006 | 251-016 | 73 | Week 24 | 3231 | 16.3 |
| | ALK21-006 | 252-009 | 81 | Week 4 | 1181 | 6.0 |
| | ALK21-006 | 252-014 | 134 | Week 4 | 741 | 3.7 |

Appendix 4: Subjects who shifted from normal CPK at baseline to high at study end (continued)

Subjects Who Shifted from Normal Creatinine Phosphokinase (U/L) at Baseline to High/3x High

| Treatment | Study ID | Subject ID | Baseline Value | Peak Week | Peak Value | Multiple of Upper Limit | |
|-----------|-----------|------------|----------------|-----------|------------|-------------------------|-----|
| 380mg | ALK21-006 | 253-002 | 135 | Week 4 | 274 | 1.4 | |
| | ALK21-006 | 253-007 | 40 | Week 4 | 349 | 2.1 | |
| | ALK21-006 | 253-013 | 169 | Week 20 | 722 | 3.6 | |
| | ALK21-006 | 253-014 | 119 | Week 8 | 354 | 1.8 | |
| | ALK21-006 | 253-015 | 92 | Week 24 | 291 | 1.5 | |
| | ALK21-006 | 253-016 | 111 | Week 16 | 337 | 2.0 | |
| | ALK21-006 | 253-020 | 78 | Week 20 | 843 | 4.3 | |
| | ALK21-006 | 253-023 | 93 | Week 20 | 224 | 1.1 | |
| | ALK21-006 | 253-025 | 43 | Week 20 | 170 | 1.0 | |
| | ALK21-006 | 253-026 | 176 | Week 12 | 350 | 1.8 | |
| | ALK21-006 | 254-003 | 197 | Week 8 | 309 | 1.6 | |
| | ALK21-006 | 254-006 | 93 | Week 20 | 208 | 1.2 | |
| | ALK21-006 | 254-009 | 112 | Week 8 | 767 | 3.9 | |
| | ALK21-006 | 255-003 | 63 | Week 24 | 173 | 1.0 | |
| | ALK21-006 | 255-004 | 72 | Week 4 | 213 | 1.3 | |
| | ALK21-006 | 255-006 | 107 | Week 4 | 281 | 1.4 | |
| | ALK21-006 | 255-021 | 96 | Week 20 | 449 | 2.7 | |
| | 190mg | ALK21-006 | 255-022 | 189 | Week 20 | 623 | 3.1 |
| | | ALK21-006 | 255-026 | 123 | Week 8 | 347 | 1.8 |
| | | ALK21-006 | 255-027 | 117 | Week 4 | 211 | 1.1 |
| | | ALK21-006 | 256-003 | 107 | Week 16 | 333 | 1.7 |
| ALK21-003 | | 202-021 | 101 | Week 20 | 170 | 1.0 | |
| ALK21-003 | | 207-001 | 121 | Week 8 | 303 | 1.5 | |
| ALK21-003 | | 209-009 | 146 | Week 16 | 244 | 1.2 | |
| ALK21-003 | | 209-013 | 105 | Week 8 | 371 | 1.9 | |
| ALK21-003 | | 210-003 | 73 | Week 20 | 200 | 1.0 | |
| ALK21-003 | | 210-012 | 144 | Week 20 | 200 | 1.0 | |
| ALK21-003 | | 210-025 | 136 | Week 16 | 226 | 1.1 | |
| ALK21-003 | | 210-033 | 139 | Week 8 | 312 | 1.6 | |
| ALK21-003 | | 211-006 | 135 | Week 16 | 215 | 1.3 | |
| ALK21-003 | | 212-018 | 125 | Week 4 | 178 | 1.1 | |

Appendix 4: Subjects who shifted from normal CPK at baseline to high at study end (continued)

Subjects Who Shifted from Normal Creatinine Phosphokinase (U/L) at Baseline to High/3x High

| Treatment | Study ID | Subject ID | Baseline Value | Peak Week | Peak Value | Multiple of Upper Limit |
|-----------|-----------|------------|----------------|-----------|------------|-------------------------|
| 190mg | ALK21-003 | 212-030 | 120 | Week 20 | 196 | 1.2 |
| | ALK21-003 | 213-004 | 102 | Week 20 | 286 | 1.4 |
| | ALK21-003 | 213-016 | 104 | Week 4 | 296 | 1.5 |
| | ALK21-003 | 213-025 | 111 | Week 12 | 195 | 1.2 |
| | ALK21-003 | 215-002 | 114 | Week 12 | 184 | 1.1 |
| | ALK21-003 | 215-017 | 165 | Week 4 | 281 | 1.4 |
| | ALK21-003 | 215-024 | 124 | Week 8 | 12609 | 74.6 |
| | ALK21-003 | 215-030 | 179 | Week 24 | 503 | 2.5 |
| | ALK21-003 | 216-001 | 192 | Week 12 | 240 | 1.2 |
| | ALK21-003 | 217-005 | 145 | Week 12 | 309 | 1.6 |
| | ALK21-003 | 217-011 | 91 | Week 8 | 710 | 4.2 |
| | ALK21-003 | 217-041 | 163 | Week 12 | 346 | 1.7 |
| | ALK21-003 | 218-002 | 107 | Week 8 | 268 | 1.4 |
| | ALK21-003 | 218-003 | 191 | Week 20 | 280 | 1.4 |
| | ALK21-003 | 224-003 | 86 | Week 20 | 208 | 1.1 |
| | ALK21-003 | 224-005 | 148 | Week 24 | 1289 | 6.5 |
| | ALK21-003 | 224-024 | 164 | Week 16 | 205 | 1.0 |
| | ALK21-003 | 226-002 | 69 | Week 8 | 228 | 1.2 |
| | ALK21-003 | 229-001 | 152 | Week 24 | 236 | 1.4 |
| | ALK21-003 | 229-004 | 193 | Week 12 | 1756 | 8.9 |
| | ALK21-003 | 229-010 | 163 | Week 16 | 257 | 1.3 |
| | ALK21-003 | 229-016 | 90 | Week 24 | 237 | 1.2 |
| | ALK21-003 | 230-015 | 102 | Week 8 | 200 | 1.2 |

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mwango Kashoki
4/5/2006 12:42:36 PM
MEDICAL OFFICER

Celia Winchell
4/11/2006 02:31:34 PM
MEDICAL OFFICER
I concur with Dr. Kashoki. See my memo.

1ST Cycle



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS
10903 New Hampshire Avenue, Silver Springs, MD 20993

Tel:(301) 796-2280

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 carboxymethylcellulose 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 | | | HAZARD RATIO (P-VALUE) | |
|------------------------------|-----|--------------------|--------|--------|------------------------|--------------------|
| | | PLACEBO | 190 MG | 380 MG | 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.

| HDD per month | Placebo | | 190 mg | | 380 mg | |
|---------------|-------------------------|------------------|-------------------------|------------------|-------------------------|------------------|
| | 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

generally innocuous tenderness, while induration and pruritis were seen commonly in the Vivitrol™-treated subjects. Injection site pain was seen most often in the higher dose group, suggesting that naltrexone itself is serving as an irritant. Depression also appeared to occur about twice as frequently in the drug-treated subjects compared to the placebo-treated subjects.

Of note, elevated eosinophil counts occurred with greater frequency in Vivitrol™-treated subjects and with the extent of elevation occurring in an apparently dose-related pattern. Additionally, all twelve cases of urticaria and angioedema occurred in Vivitrol™-treated subjects.

Medication Errors:

The Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety has recommended that the Vivitrol™ Kit not contain the proposed three syringe needles (i.e., two 20-gauge 1 ½ inch and one 20-gauge ½ inch), as “This may cause confusion and error as healthcare practitioners may inadvertently use the 1 ½ inch needle for reconstitution and then switch to the shorter ½ inch needle for the intramuscular (IM) injection. Additionally, some practitioners may not switch the needles prior to administration.”

I do not agree with this speculative scenario. Physicians, nurses and other health-care practitioners are quite familiar with the need to use a longer needle for a gluteal IM injection. The longer needle would also make transfer of the diluent more difficult.

Nonclinical Safety:

Dr. De has recommended that this application should not be approved at this time due to the absence of adequate evidence that the exposure (toxicokinetic data) in the referenced naltrexone preclinical studies provides support for the higher exposures found in the clinical pharmacokinetic studies for Vivitrol™ compared to the oral formulation, and the consequent need for the sponsor to perform Segments I, II and III reproductive toxicity studies and carcinogenicity studies in two species. However, Dr. Mellon has recommended that the application is approvable. While he concurs with Dr. De that there is currently inadequate preclinical support for the naltrexone exposure levels found with Vivitrol™, he has concluded that the sponsor may be able to perform a bridging study that will allow interpretation of the relative exposure to naltrexone between the existing animal and human studies, thereby obviating the need for additional toxicology studies. If the sponsor is unable to document adequate preclinical support for the higher exposure levels based on this bridging study, he recommends that the reproductive toxicology studies and the carcinogenicity studies would then be required.

Dr. Mellon has also determined that the references to products other than Revia cited in this application are not necessary for a determination of the preclinical safety of Vivitrol™ and, therefore, the absence of patent certification and relative bioavailability studies for these references is moot.

Biopharmaceutics:

Dr. Nallani has concluded that the application is approvable if the sponsor agrees to provide revisions to the drug release specifications to include the addition of appropriate Day 14 and Day 28 drug-release information. In addition, he recommends that the sponsor should be required to agree to the following Phase 4 commitments:

- conduct in vitro CYP inhibition studies using conventional substrates, as the data submitted in the application were drawn from studies employing fluorescent substrates which tend to introduce non-specificity in detection, and;
- conduct in vitro studies in human hepatocytes to evaluate the potential of naltrexone to induce CYP3A4 and CYP1A2.

It is important to note that Dr. Nallani has also determined that Vivitrol™ has, on average, a 4-fold greater AUC than the oral formulation of naltrexone.

Chemistry, Manufacturing and Controls:

Dr. Boal has concluded that the application is approvable based on the CMC data submitted, but that the sponsor should agree to the following Phase 4 commitment:

- Assess the in vitro drug release data and percent crystallinity for the first five commercial batches in order to tighten the ranges for the in vitro drug release specifications and _____ the percent crystallinity of naltrexone in the microspheres.

Discussion:

The sponsor has provided evidence that Vivitrol™ is effective for the treatment of alcohol dependence, but only in patients who are abstinent for seven days at the initiation of treatment. While there was a numerical trend supportive of non-abstinent subjects being responsive to treatment with Vivitrol™, the overwhelming source of the statistically significant treatment effect found in the primary outcome analysis came from the abstinent-at-baseline subjects. This finding was also supported by the responder analyses.

Vivitrol™ appears to have a significantly more concerning adverse event profile compared to the approved oral formulation of naltrexone. The most concerning set of adverse events that appear to be unique to this formulation are those related to the immune system: a notably high frequency of peripheral eosinophilia and frequent skin reactions (one quite serious, requiring extensive tissue excision) in Vivitrol™-treated subjects; twelve cases of urticaria and angioedema occurring only in Vivitrol™-treated subjects; and one case of apparent eosinophilic pneumonia in a subject treated with Vivitrol™. I concur with our own expert consultants from DPAP that these findings do not represent clear evidence of a specific immunologic effect. However, the presence of all of these abnormalities, especially the presence of the notable case of probable eosinophilic pneumonia, an extremely rare and life-threatening disorder when not treated quickly and appropriately, has raised a high level of concern regarding the safety of this product.

In light of these safety concerns, we must consider the risk:benefit ratio for the to-be-treated patient population. As noted above, the likelihood of achieving effective treatment with Vivitrol™ appears to be differentially related to drinking status at the initiation of treatment. Abstinent patients have a relatively high degree of success and, thus, the benefits associated with treatment would likely outweigh the risks associated with untreated alcoholism. However, it is unclear whether Vivitrol™ is truly effective in non-abstinent patients

A handwritten signature in black ink, consisting of several distinct, slanted strokes.

In addition to the clinical safety concerns noted above, the sponsor has not provided adequate preclinical support for the naltrexone exposure levels found with Vivitrol™. Due to the fact that Vivitrol™ results in a 4-fold higher exposure to naltrexone compared to the approved oral formulation, it will be necessary for the sponsor to provide data from a bridging toxicokinetic study that will allow interpretation of the relative exposure to naltrexone based on the currently existing animal and human studies, thereby obviating the need for additional toxicology studies. If, however, the sponsor is unable to document adequate preclinical support for the higher exposure levels based on this bridging study, reproductive toxicology studies and carcinogenicity studies would then be required.

Action: Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
12/23/2005 04:06:31 PM
MEDICAL OFFICER

1ST Cycle



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

MEMORANDUM

DATE: December 20, 2005

TO: File, NDA 21-897

FROM: Celia Jaffe Winchell, M.D.
Medical Team Leader

RE: Supervisory Review of NDA 21-897
Medisorb Naltrexone (Vivitrol)
Alkermes, Inc
Submitted 3/31/2005

| | | |
|-------|--|----|
| 1 | Background | 2 |
| 1.1 | Discussion of Efficacy Endpoints | 3 |
| 1.1.1 | The Timeline Follow-back Method | 4 |
| 1.2 | Important Safety Issues | 5 |
| 1.3 | Priority Review Status | 5 |
| 2 | Effectiveness | 6 |
| 2.1 | Overview | 6 |
| 2.2 | Population | 6 |
| 2.3 | Design and Endpoints | 6 |
| 2.4 | Outcome Measures and Analytic Approaches | 7 |
| 2.5 | Results | 8 |
| 2.5.1 | Demographics and Patient Disposition | 8 |
| 2.5.2 | Efficacy Results | 10 |
| 2.5.3 | Event Rate of Heavy Drinking | 10 |
| 2.5.4 | Responder Analysis | 12 |
| 2.5.5 | DSI Inspection Issues and Reanalyses | 14 |
| 2.5.6 | Efficacy Conclusions | 15 |
| 3 | Safety | 16 |
| 3.1 | Exposure | 16 |
| 3.2 | Deaths | 17 |
| 3.3 | Serious Adverse Events | 17 |

| | | |
|-------|--|----|
| 3.4 | Discontinuations | 18 |
| 3.5 | Other Significant Adverse Events..... | 19 |
| 3.5.1 | Hepatic Effects..... | 19 |
| 3.5.2 | Injection Site Reactions | 21 |
| 3.5.3 | Psychiatric Events..... | 22 |
| 3.6 | Events Suggestive of Allergic Response | 23 |
| 3.7 | Common Adverse Events | 25 |
| 3.8 | Laboratory Data | 29 |
| 3.9 | Vital Signs, Weight..... | 29 |
| 3.10 | Off-Label Safety in Opiate Abusing Population..... | 29 |
| 4 | Discussion of Safety and Efficacy Issues | 29 |
| 5 | Pre-Clinical Issues | 30 |
| 6 | Chemistry, Manufacturing, and Controls Issues..... | 30 |
| 7 | Clinical Pharmacology Issues | 31 |
| 8 | Nomenclature Issues | 32 |
| 9 | Conclusions and Recommendations | 32 |

1 BACKGROUND

Naltrexone is an antagonist at the μ -opiate receptor. An oral formulation of naltrexone was approved in 1984 for the indication “for the blockade of effects of exogenously-administered opioids”¹ and a subsequent efficacy supplement was approved in 1994 adding an indication “in the treatment of alcohol dependence,” noting that “ReVia has not been shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions.”

The approval of naltrexone tablets, marketed as ReVia, for the treatment of alcohol dependence, was based on two investigator-initiated studies. Neither was reviewed prospectively by the Agency, and no one specific primary endpoint was required. The study population in both studies were alcoholics who were abstinent at study entry, and the analyses showed that more naltrexone-treated subjects than placebo-treated subjects maintained their abstinence over the 12-week observation period. Both studies are in the published medical literature.

The incorporation of naltrexone into the treatment of addiction in clinical practice has been not entirely enthusiastic. A general impression that the efficacy is limited has been bolstered by the publication of several negative studies. However, it has been generally believed that poor compliance plays a role in limiting the effectiveness of oral naltrexone in addiction treatment. Therefore, the development of passive-compliance formulations

¹ This indication was approved after advisory committee consultation when a program of clinical trials in opiate addiction treatment failed to demonstrate efficacy. The pharmacologic effect was well-established, but, as the label notes, “there are no data that demonstrate an unequivocally beneficial effect of REVIA on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug.” Note that the original proprietary name was Trexan; the name was changed to ReVia at the time of the approval of the alcoholism treatment supplement.

(implants, transdermals, depot injections) is a logical extension of the development of naltrexone.

Alkermes is seeking to develop a depot formulation of naltrexone. The Alkermes product consists of microspheres of naltrexone incorporated into a biodegradable matrix of polylactide-co-glycolide (PLG) and a diluent, intended for intramuscular injection. PLG is a biodegradable medical polymer which is used in other FDA-approved products.

The development program has been very focused. Rather than developing the product for use in both indications carried by oral naltrexone, the applicant focused on seeking approval in only one of the two indications (alcoholism), and on identifying an efficient pathway to approval. Alkermes carried out a development plan that included only a single efficacy study, with the aim of seeking approval under section 505(b)(2), making reference to the Agency's previous finding of efficacy for oral naltrexone.

The previous agency finding of efficacy for oral naltrexone was based, as noted above, in two studies in alcoholic subjects abstinent at study entry. Notably, the labeling does not describe this feature of the studies or stipulate that patients should be abstinent at treatment initiation. Multiple outcome measures were analyzed, but compelling measures such as the rate of complete abstinence throughout treatment, and the rate of non-relapse (defined as never having a heavy drinking day throughout treatment) supported the drug's efficacy.

1.1 Discussion of Efficacy Endpoints

One of the most difficult aspects of the development program for this product was that it took place during a time of evolving thinking about outcome measures for alcoholism treatment trials. Conventional wisdom has long held that, for alcoholics, the target level of alcohol consumption is complete abstinence from alcohol, and that only this outcome represents successful alcoholism treatment. This recommendation is made notwithstanding the observation that the consumption of limited quantities of alcohol may actually confer health benefit. However, it has been observed that sustained, controlled drinking at low levels does not appear feasible for the alcoholic patient. However, it should be recognized that this feature of alcoholism may be amenable to treatment (perhaps pharmacologic treatment in particular), and therefore studies may be designed to define other patterns of drinking behavior, short of complete abstinence, as successful.

While recognizing that some outcome measure other than the proportion of subjects not drinking at all (complete abstinence) might be desirable, the Division had, for a period of time, little access to empirically-based recommendations for alternative outcome measures. Recently, at the FDA's request, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) contracted for exploratory analyses of two existing datasets to try to establish some data-supported recommendations regarding drinking patterns that could be considered non-risky. If these patterns could be identified, any subject in an

alcoholism treatment study who exhibited one of these patterns might be termed successful. The results of these analyses, still preliminary, have only recently become available, but they converge on a common recommendation. It appears that individuals who drink occasionally, but never heavily, are at very low risk of experiencing the adverse social and occupational consequences of alcohol use, even if those individuals have a history of alcohol problems. Although the proportion of patients achieving and maintaining complete abstinence from alcohol drinking remains an endpoint of indisputable significance, evidence suggests that the proportion of patients able to maintain a non-risky drinking pattern would be of similar significance. Although several definitions of risky drinking have been proposed, the analyses available support the recommendation that any day on which *more than four standard drinks of alcohol* are consumed, for male subjects, or on which more than three standard drinks of alcohol are consumed, for female subjects, is considered a heavy drinking day. Evidence suggests that the strongest predictor of avoiding consequences of alcohol use is the absence of *any* heavy drinking days in the observation period (ranging from 3 – 12 months in these analyses).

More liberal definitions of success could be constructed, allowing for one or more violations of this quantity limit, but the analyses suggest that even one heavy drinking day over a several month period appreciably increases the risk of alcohol-related consequences, and that “commonsense” cutoffs such as two heavy drinking days per week (i.e. on weekends) are associated with substantial alcohol-related problems. It may well be the case that the risk of consequences is reduced from pre-treatment levels if individuals can cut back from near-daily heavy drinking to lower frequencies without eliminating heavy drinking altogether. However, this conclusion requires further analysis of the available information. The most compelling conclusion of the analyses so far is that individuals—even those with a history of alcoholism treatment—can essentially avoid consequences if they avoid drinking heavily.

Thus, an empirically-supported definition of treatment success that does not require complete abstinence would be the absence of any heavy drinking days during the observation period. A study could be designed with a grace period to allow for patients to gain control of their drinking with the help of the pharmacologic and non-pharmacologic treatments provided in the study, or patients could be abstinent at randomization (perhaps by virtue of completing a program of detoxification).

This information was not available at the time the sponsor and agency were discussing the protocol for the single efficacy study submitted in support of this application. However, the data collected and the basic design allow for this analytic approach to be applied, so that the effect of the study drug can be explored using these empirically-supported endpoints.

1.1.1 The Timeline Follow-back Method

The instrument used to collect the drinking behavior data in the efficacy study was a method known as the Timeline Follow-back Method (TLFB). Using a calendar and

various memory aids, subjects are assisted in filling in retrospective estimates of their daily drinking over a specified time period. This instrument has been used extensively for over twenty years in both research and clinical settings. It can be used in a clinical setting when administered by the therapist to help the patient explore patterns in drinking behavior and identify antecedents and consequences of drinking. In a research setting, data may be collected by a trained interviewer or the instrument can be self-administered in either a paper-and-pencil or computerized format. In the face-to-face interview method, techniques are used by the interviewer to help the subject recall the specific number of drinks consumed on a given occasion. The nature of these techniques and the uncertainty of the subject may offer the opportunity for the interviewer to have some influence in what is ultimately reported.

The administration of the instrument by a person who also serves as the subject's therapist or counselor may affect the results either by introducing motivation to please the therapist (by minimizing reports of drinking), or by actually providing therapeutic benefit as noted above. It is important that interviewers administering the TLFB be blind to treatment assignment to prevent unintentional introduction of bias. Furthermore, it is desirable that the TLFB information be collected in a consistent manner—either by the therapist or by a non-therapist staff member, so that the effect of having the therapist collect the data, if any, applies across all study participants.

1.2 Important Safety Issues

Three specific safety issues were identified as important for Alkermes to address during development. The first of these was the hepatic safety Medisorb Naltrexone, which was of concern due to statements included in the labeling of oral naltrexone. Second, the psychiatric adverse event profile of Medisorb Naltrexone was of concern due to the possibility that blockade of opioid receptors and possible interference with endogenous opioids could cause dysphoria and potentially elevate the risk of depression and suicide. Finally, although Alkermes sought approval only for the alcoholism indication, oral naltrexone is approved for, and used in, opiate dependence as well. Opioid addicts who attempted to overcome the blockade of μ -receptors by escalating their dose of illicit opioids could be at risk of overdose. Alkermes was asked to collect safety data in this population.

1.3 Priority Review Status

This application was assigned priority review status on the basis of Alkermes' claim that the Medisorb formulation represented an improvement in safety over the available formulation of naltrexone. Based on several theoretical arguments why the depot formulation would present a lower risk of hepatic effects (lower total monthly dose, avoidance of first-pass metabolism), the Division agreed to review the application under a priority timeline. A major amendment (reanalysis of efficacy data submitted after concerns were identified during inspection by the Division of Scientific Investigation) extended the clock to 9 months.

2 EFFECTIVENESS

Only one efficacy study was included in this application. The application was intended to rest partially on the Agency's previous finding of efficacy for oral naltrexone, and appropriate information was provided to incorporate this finding through the 505(b)(2) application mechanism. However, there did exist some uncertainty about whether the effectiveness of naltrexone would be maintained without the peaks and troughs of oral dosing, and with a very different ratio of parent to metabolite than that seen after oral dosing.

2.1 Overview

The single study submitted in support of efficacy was Study ALK21-003, a randomized, double-blind, and placebo controlled trial in adults who met DSM-IV criteria for alcohol dependence. Patients were treated with study drug (Medisorb Naltrexone (190-mg or 380-mg) or placebo) for 6 months.

2.2 Population

To be eligible, patients were required to meet DSM IV diagnostic criteria for alcohol dependence, and had to have had at least 2 episodes of heavy drinking per week during the 30 days prior to screening (or prior to detoxification, if patients entered the trial after a period of detox). Patients were excluded for significant medical illnesses or lab abnormalities (AST/ALT >3x upper limit of normal, elevated INR or bilirubin), significant psychiatric diagnoses, other drug dependence diagnosis, use of prohibited medications (including, but not limited to, benzodiazepines, acamprosate, disulfiram, oral naltrexone, anticonvulsants). Patients could begin screening as much as 14 days prior to randomization; patients requiring medical treatment of alcohol withdrawal were required to complete detoxification by Day -7.

2.3 Design and Endpoints

Eligible subjects were randomized to one of four treatment conditions in a 2:2:1:1 ratio. Treatments included:

- Medisorb Naltrexone 380 mg (4 ml injection)
- Medisorb Naltrexone 190 mg (2 ml injection)
- Placebo for 380 mg (4 ml vehicle injection)
- Placebo for 190 mg (2 ml vehicle injection)

Study medication was to be administered every four weeks as an intramuscular injection in the gluteal muscle, with sites of administration alternating left/right.

Study visits were scheduled to occur weekly for the first month, bi-weekly for the next two months, and then every four weeks for the last three months, with telephone contact occurring at the two-week mark between visits. At each visit and telephone contact, drinking data was to be collected using the TLFB method. The amount of alcohol

consumed was converted into a number of standard drinks using a protocol-specified definition/formula.

Psychosocial treatment was provided using an approach developed for use in primary-care settings, known by the acronym **BRENDA** (Biopsychosocial, Report, Empathy, Needs, Direct advice, and Assessment of responsiveness). BRENDA is a brief therapy model focusing on compliance with medication, and using motivational techniques to change addictive behaviors. The BRENDA model was developed at the University of Pennsylvania as a psychosocial intervention for alcohol dependence to complement the use of pharmacotherapies such as naltrexone. Treatment is delivered by a nurse or nurse-practitioner. The BRENDA approach has not previously been used in studies supporting regulatory approvals of addiction treatments, but was deemed acceptable by the Division during the IND review process. Twelve sessions of BRENDA therapy were included in the protocol. The protocol specified (under Amendment #2) that the BRENDA therapy and the collection of TLFB data were to be conducted by different individuals.

2.4 Outcome Measures and Analytic Approaches

The protocol-specified primary outcome analysis was the event rate of heavy drinking using the Andersen-Gill model. A heavy drinking event was defined as at least 4 drinks/day (women) and 5 drinks/day (men). The event rate was to be calculated over the duration of treatment (i.e. over 24 weeks or up to the time of treatment discontinuation). In the analysis, patients randomized to either volume of placebo (2-mL or 4-mL) would be combined to form one placebo group.

A number of secondary analyses of drinking patterns were also pre-specified, including responder analyses requested by the division.

The primary analysis of the primary endpoint did not include imputation would be performed for days in which drinking data were unavailable. Specifically, a counting process style of data input to the Cox model was used. Each subject contributed drinking event intervals (in days) for the days in which data were collected. Time for which data were not collected was not included in any of the intervals. At the Division's request, Alkermes performed a sensitivity analysis where subject that were missing in the middle of the study (i.e. before a subject completed or discontinued) were imputed as heavy drinking days.

As noted above, after reaching agreement with Alkermes that the event rate of heavy drinking could be used as a primary analysis (supported by secondary analysis of responder rates), the Division became aware of data developed by NIAAA which provided empirical support for the selection of a responder definition based on drinking patterns. Understanding that any analysis based on alcohol consumption is a surrogate endpoint (true clinical benefit in the form of improved psychosocial, occupational, or physical well-being is not measured and is unlikely to be captured in a six-month study), the availability of a responder definition that appears to be an appropriate surrogate for

clinical benefit prompted the division to give greater attention to the analyses which were originally designated as secondary.

2.5 Results

2.5.1 Demographics and Patient Disposition

A total of 624 patients were randomized to treatment and received at least one dose of study medication: 210 in the Medisorb Naltrexone 190 mg group, and 205 in the Medisorb Naltrexone 380 mg group. The placebo group included 209 patients, divided between the 2 ml and 4 ml placebo groups (these groups, which received diluent+microspheres without naltrexone, were later combined for most analyses).

Baseline characteristics were similar for the 3 treatment groups. Mean age was 44.7 years with a range of 19-79 years. The proportion of males to females was approximately 2:1 for all treatment groups. Most subjects were Caucasian (83.5%).

The majority of subjects (571, 91.5%) reported lead-in drinking during the week prior to treatment initiation. During the 30 days prior to the first dose, subjects reported a mean of 22.9 drinking days, and a mean of 19.5 heavy drinking days (with a range from 0 to 30). This corresponds to a mean of 76.4% drinking days and 64.9% heavy drinking days over that one month period. Treatment goals were similar among treatment groups. Nearly three quarters of subjects reported baseline treatment goals of total abstinence (43.3%) or occasional use (30.6%). Nearly half of the subjects (48.6%) were enrolled at an addiction treatment center; 34.0% enrolled at a research center; and 17.5% enrolled at a combination addiction/research center. Severity of alcoholism was assessed using the Alcohol Dependence Scale (ADS) for patients randomized after April 2002 (about half the population). The mean score was 17-18% across treatment groups, with a range of 1 to 42 (maximum possible score is 47).

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Patient disposition is illustrated in the table below².

Patient Disposition, Study ALK21-003 (from Dr. Kashoki's Table 10.1.1.d)

| | Placebo | | | Medisorb Naltrexone | |
|--|---------|---------|----------|---------------------|----------|
| | 2 mL | 4 mL | Pooled | 190-mg | 380-mg |
| N Dosed | 105 | 104 | 209 | 210 | 205 |
| N(%) ¹ completed treatment | 62 (59) | 73 (70) | 135 (64) | 137 (65) | 130 (63) |
| Reason ³ for discontinuation, N(%) ¹ | | | | | |
| Lost to follow-up | 19 (18) | 9 (9) | 28 (13) | 31 (15) | 24 (12) |
| Adverse events | 7 (7) | 6 (6) | 13 (6) | 12 (6) | 27 (13) |
| Subject withdrew consent | 8 (8) | 5 (5) | 13 (6) | 14 (7) | 15 (7) |
| Lack of efficacy | 7 (7) | 9 (9) | 16 (8) | 9 (4) | 9 (4) |
| Investigator judgment | 1 (1) | 1 (1) | 2 (1) | 2 (1) | 0 |
| Protocol violation | 0 | 0 | 0 | 2 (1) | 0 |
| Other [#] | 1 (1) | 1 (1) | 2 (1) | 3 (1) | 0 |

¹ Percentages are out of number of subjects dosed

³ Reason for discontinuation was reclassified using all applicable information on each subject

[#] "Other" includes: incarceration (n = 2); too far out of dosing window to receive an injection (n = 3)

As shown above, discontinuation due to adverse events was more than twice as common in the 380 mg dose group than in the other groups (13% vs. 6%). Conversely, discontinuation due to lack of efficacy was twice as common in the placebo group vs. either treatment group (8% vs. 4%).

The extent of exposure and treatment retention in the study is illustrated in the table below, taken from Dr. Kashoki's Table 10.1.1.e:

| # of injections received | Placebo | Medisorb Naltrexone | |
|--------------------------|-----------|---------------------|-----------|
| | | 190 mg | 380 mg |
| 1 dose | 15 (7%) | 23 (11%) | 19 (9%) |
| 2 doses | 25 (12%) | 18 (9%) | 25 (12%) |
| 3 doses | 9 (4%) | 13 (7%) | 14 (7%) |
| 4 doses | 18 (9%) | 12 (6%) | 8 (4%) |
| 5 doses | 8 (4%) | 7 (3%) | 9 (4%) |
| 6 doses | 134 (64%) | 137 (65%) | 130 (63%) |

The mean days from first to last dose ranged from 107-110 days across groups, with a median of 140 days in each group.

² This table was compiled after re-adjudicated data was submitted at Dr. Kashoki's request. Original patient disposition tables failed to identify subjects who discontinued study medication but remained in the trial, and also identified some patients who discontinued due to lack of efficacy (i.e. relapse to alcoholism) as discontinuations due to AEs.

2.5.2 Efficacy Results

The analyses below describe several approaches to the efficacy data. First, the applicant's primary analysis, the event rate of heavy drinking. Then, to understand the clinical significance of the effect of naltrexone on this variable, several other analyses were undertaken. Responder analysis is considered a very important tool for evaluating the ability of the treatment to yield clinically-compelling improvements in the status of individual study participants; this is of particular importance in assessing the risk/benefit ratio of a product. Although the applicant did conduct responder analyses, several aspects of their calculations were unsatisfactory (as described below). Therefore, responder analyses, using various response definitions, were carried out by Dr. Dionne Price. Additionally, because of the lack of prior information about the effect of naltrexone in subjects drinking at baseline, Dr. Price also examined (using both responder analyses and event rate analysis) the effect of naltrexone on the subgroups of patients who were abstinent for the seven days before treatment initiation and the patients who were drinking.

For the purposes of these analyses, different definitions of "heavy drinking" could be used. Several different analyses were performed, employing either a definition of 5 drinks on a single day (or more) for men/4 drinks or more for women, or the more stringent ≥ 4 drinks for men/ ≥ 3 drinks for women. Similar results were found with either analysis; therefore only the $\geq 5/\geq 4$ analysis is illustrated below.

2.5.3 Event Rate of Heavy Drinking

Dr. Price's review provides an explanation of the method used for calculation of the primary outcome variable. In brief (excerpted from her review):

Since the event of interest (i.e. heavy drinking) could occur on multiple days, the statistical methodology used by the applicant accounted for recurrent events across time. Specifically, an Anderson-Gill model was used to assess the overall effect of treatment. The model was stratified using the randomization factors of gender, treatment goal of abstinence, and abstinence at baseline (i.e. no drinking seven days prior to the initial treatment administration). In general, the Anderson-Gill model is formulated by dividing the follow-up time for each patient into intervals defined by actual heavy drinking days. Thus, a patient only contributes data (and belongs to the risk set) for the days having a recorded measurement of the number of drinks consumed. The model assumes that multiple observations per patient are independent and does not differentiate the first event from the second event and so on. Furthermore, another assumption of the model is that of proportional hazards (i.e. the hazard or risk of experiencing a heavy drinking day is constant).

Event rates obtained via the Anderson-Gill model were based on available data only. The applicant assumed that uncaptured or missing data occurred randomly and provided no additional insight into the effect of the treatment. To assess the assumption that missing data occurred randomly, the applicant examined the comparability of the treatment groups for subject discontinuation and outcomes

via several techniques. The applicant examined the event rate of heavy drinking by the number of doses received, the Kaplan-Meier curves, and a pattern mixture model. In general, a pattern mixture model is a statistical tool designed to model the available or observed data and the missing data mechanism. Using the pattern mixture model approach employed by the applicant, the data was initially stratified by the number of doses (i.e. the missing data pattern). Estimates of the high and low dose treatment effects were then obtained within each stratum. The estimates were subsequently weighted (by 1/variance), and pooled estimates and variances were obtained to formulate conclusions. In the construction of a general pattern mixture model, strata are selected by combining groups with similar missing data patterns. Moreover, an assumption of the approach is that uncaptured data within each stratum is missing randomly.

The results of the applicant's primary analyses are depicted in below, in Dr. Price's Table 3. The applicant concluded that the 380 mg dose of Medisorb Naltrexone significantly reduced the event rate of heavy drinking as compared to placebo. Specifically, patients receiving 380 mg of Medisorb Naltrexone experienced a 25% reduction in the event rate of heavy drinking compared to the placebo group. It should be noted that all groups, including the placebo group, demonstrated marked improvements from baseline. In the comparisons below, the hazard ratios indicate the difference between the improvements seen in the placebo group and the improvements seen in the treatment groups.³

Event rate of Heavy Drinking*†: Test for Treatment Effect in ALK21-003:
Anderson-Gill (Robust Variance) Stratified Analysis
(Source: Reproduced from Final Study Report ALK21-003, Table 8)

| | Estimate | Hazard ratio (95% CI) | Unadjusted p-value | Adjusted p-value |
|-----------------------|----------|--------------------------|-----------------------|---------------------|
| 190 mg vs. placebo | -0.186 | 0.830 (0.677,1.018) | 0.0744 | 0.0744 |
| 380 mg vs. placebo | -0.287 | 0.751 (0.600,0.940) | 0.0123 | 0.0245 |

For each variable (190mg or 380 mg) in the analysis, parameter estimates are obtained for each stratum and pooled by weighting each stratum by 1/var (as described by Wei and Johnson, Biometrika, 1985)

†Hochberg method was used to adjust p-value of 190 vs. placebo and 380 mg vs. placebo.

Dr. Price explored the effects of various assumptions in the applicant's analysis and concluded that the study provided evidence of a treatment effect of Medisorb Naltrexone.

Because experience with naltrexone treatment has suggested that its efficacy may be limited, perhaps to specific sub-populations, and because previous studies were done in patients abstinent at treatment initiation, I was particularly interested in determining whether this analysis, considered more powerful than the various responder analysis

³ Median heavy drinking days per month, as calculated by Dr. Price, imputing missing days as heavy drinking days, were 19.3 at baseline (groups combined). During treatment, the median value for heavy drinking days per month was 10.5 for the placebo group, 9.1 for the 190 mg group, and 6.2 for the 380 mg group.

approaches, demonstrated an effect of naltrexone in patients drinking at baseline. The table below summarizes results of subset analyses conducted by the applicant to explore the effect of naltrexone in patients abstinent at baseline vs. those drinking at baseline. For the purposes of these analyses, “abstinent at baseline” patients were those who reported no drinking during the 7 days prior to the first injection. Although some patients underwent detoxification prior to enrolling in the study, per protocol, detox had to be completed by day -7, therefore, all of the subjects who abstained for the week prior to the first injection did so on their own, not through participation in a detoxification program. The applicant also explored the influence of the patients’ own stated goals for treatment, based on a multiple-choice assessment in which patients could identify their goals to be “total abstinence” or several other options. Some in the alcoholism research treatment field have identified this as a potential prognostic factor of importance.

As shown in the table below, treatment goal was not a major factor in determining outcome, with hazard ratios (representing the comparison of the extent of reduction in the event rate of heavy drinking between the treatment group and placebo) fairly similar in both patients who aspired to abstinence and those who did not. However, a very striking finding was the overwhelming importance of the participants drinking *behavior* during the week prior to treatment initiation. Although only 53 study participants were abstinent from drinking during that time, the hazard ratios demonstrate that either dose of Medisorb Naltrexone was associated with a very substantial improvement over placebo in the event rate of heavy drinking, and that even with fewer than 20 subjects per group, statistical significance with a very small p-value was reached in this subgroup. In contrast, only a hazard ratio of .79 was seen in the patients who consumed alcohol in the week prior to treatment initiation.

| FACTOR | LEVEL | NUMBER OF SUBJECTS | | | HAZARD RATIO (P-VALUE) | |
|------------------------------|-------|--------------------|--------|--------|------------------------|--------------------|
| | | PLACEBO | 190 MG | 380 MG | 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) |

(from Sponsor’s Table)

To understand whether this effect on the event-rate of heavy drinking, particularly in the non-abstinent subset, represented clinically meaningful improvements in drinking patterns on an individual level, we gave attention to the responder analyses discussed below.

2.5.4 Responder Analysis

As noted above, in the time intervening between the submission of the protocol for ALK21-003 and the review of the NDA, the Division became aware of analyses conducted by NIAAA which provided a link between various patterns of drinking

behavior and the likelihood of drinking-related psychosocial consequences. These analyses could be undertaken to explore whether the “reduction in the event rate of heavy drinking” captured in the primary analysis reflected a substantial clinical improvement for naltrexone-treated patients. Recognizing that the study was not powered for these endpoints, the clinical review team nevertheless felt that the results were illustrative even without formal statistical comparisons.

Alkermes performed a responder analysis of their own; however, in their analyses, although the tabulations purported to describe the proportions of patients drinking heavily on 0, 1, 2, 3, or 4 days per month, in actuality, the proportions were constructed using “average” drinking patterns, so that a patient reporting 24 heavy drinking days was described as drinking an “average” of 4 days per month, even if these days all occurred in the same month. In addition, no imputation of missing data was performed in their analyses. Therefore, I did not find their tabulations to be informative and did not reproduce them here. Dr. Price constructed a number of tabulations of responders at the clinical team’s request. These are shown below. To address the hypothesis that naltrexone works by reducing the reward experienced when alcoholics consume alcohol, we allowed for a “grace period” in the analysis, during which patients who sampled alcohol and found it unrewarding, such that future drinking episodes were curtailed, would not be counted as treatment non-responders.

The table below illustrates the range of responses in the study population as a whole. As seen below, very few subjects achieved a complete absence of any heavy drinking days, and no effect of naltrexone treatment is apparent when the rates are inspected. Even using more and more “liberal” definitions of treatment success, only very small numerical differences in the proportions of successful subjects are seen across treatment groups. P-values were not included in the table, as Dr. Price cautioned that formal statistical inference is considered inappropriate in examining these data presentations.

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%) |

The table below explores the effect of abstinence at baseline, separating subjects into those who reported drinking during the week prior to treatment initiation (non-abstinent) and those who reported no drinking (abstinent).

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

| HDD per month | Placebo | | 190 mg | | 380 mg | |
|---------------|----------------------------|---------------------|----------------------------|---------------------|----------------------------|---------------------|
| | 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%) |

Again, the contrast is striking between the two subgroups. In the 91% of patients who did not abstain from alcohol during the week prior to treatment initiation, only 35% or the 380 mg group could be considered treatment successes, even using a very liberal definition of success, in which all drinking behavior during the first two months of treatment was ignored altogether and as many as 16 heavy drinking days during the remainder of the study could occur. While this is somewhat higher than the 26% of the placebo group that met that standard, it is not compellingly so, and the treatment effect is less apparent at more stringent (and therefore more clinically compelling) definitions of success. In contrast, the success of the very small subgroup who were abstinent at baseline is impressive and the treatment effect obvious, even using the most stringent and clinically compelling success definition, complete absence of heavy drinking days. In fact, this analysis suggests that both doses may be effective,

I also asked Dr. Price to analyze the proportion of patients who did not drink at all, to see whether the responder definition which considered all non-heavy drinking ignorable led to a different conclusion than defining a responder as being completely abstinent. In the “abstinent at baseline” subset, about a third of responders were in the “controlled drinking” category (i.e., drank, but did not drink heavily), with no effect of naltrexone treatment apparent. In the “drinking at baseline” subgroup, after a two-month grace period, about 40% of the patients considered “responders” were patients who did consume alcohol, but never reported a heavy drinking day. However, this category was more prevalent among the placebo-treated patients than the naltrexone-treated patients, offering no support for the contention that naltrexone works by promoting control in patients who drink.

2.5.5 DSI Inspection Issues and Reanalyses

The inspection of clinical sites by the Division of Scientific Investigations identified some protocol violations of potential importance. Notably, although the protocol stipulated that the TLFB data should be collected by a staff member other than the BRENDA therapist, instances of TLFB data collected by the BRENDA therapist were identified at two of the five sites inspected. Because of the possibility that patients might

report differently to a therapist than to a staff member not involved with treatment, we were concerned about the effect of these events. Initially, we asked Alkermes to reanalyze the efficacy data with the two sites excluded, and noted that, without these sites, the study no longer provided evidence of efficacy on the primary endpoint.

However, on further consideration, the review team determined that excluding the two affected sites from analysis was not a rational approach to the problem, as it was very likely violations of this type occurred at many of the sites that were not inspected. Furthermore, the violations were sporadic and affected only some of the subjects at some of their visits. It was impossible to determine whether this deviation from the protocol-specified method of data collection could introduce bias into the study; in any case, it would not be logical to exclude data from only the two sites where this was known to have occurred and include data from all other sites where similar problems probably existed.

Thus, no change in the analysis was made as a result of the DSI findings, but general confidence in the accuracy of the data was somewhat lessened by DSI's observations. Notably, DSI's inspection identified many examples of non-adherence to protocol; these were the only ones felt significant enough to merit exploration of their impact on the interpretation of the results.

2.5.6 Efficacy Conclusions

In conclusion, while the primary analysis of "event rate of heavy drinking" provides evidence of a treatment effect of Medisorb Naltrexone, these explorations elucidate that the treatment effect in patients who are unable to refrain from drinking for a week prior to treatment initiation is quite modest and may not outweigh the risks of the treatment.

While it is tempting to recommend approval of the product for patients who are abstinent at baseline, I note that this is the sole study in support of this product. I cannot recommend approval based on a post-hoc subset analysis of a single efficacy study, albeit bolstered by previous agency finding concerning the active moiety given by a different route. Further elucidation of the efficacy of this product in recently-detoxified individuals would be optimal, in order to establish whether it is effective only in patients with a low level of severity of alcoholism who can abstain spontaneously for a week, or whether it can also be effective in severely dependent alcoholics, as long as abstinence can be enforced prior to treatment initiation.

3 SAFETY

The safety database appears to have been of sufficient size and the monitoring procedures appear to have been appropriate to characterize the safety profile of Medisorb Naltrexone. The safety data was coded using the Medical Dictionary for Regulatory Activities (MedDRA). Tabulations illustrating safety by System Organ Class (SOC) and Preferred Term were provided by the sponsor, but the granularity of the classification system required extensive reanalysis by Dr. Kashoki to discern patterns by combining like terms. Her methods and the specific terms used in her analyses are included in her review. Overall, she determined that treatment with Medisorb Naltrexone was most commonly associated with injection site reactions, gastrointestinal effects, headache, dizziness, and somnolence. Medisorb Naltrexone injections were also more likely than placebo to be associated with asthenia, arthralgia, and muscle cramps. Medisorb Naltrexone appears to have allergic potential, causing reactions such as inflammatory-type injection reactions, eosinophilia, urticaria, and angioedema. Depression and, to a lesser extent, suicidality, may be a risk of Medisorb Naltrexone treatment. Notably, few significant hepatic abnormalities were associated with Medisorb Naltrexone treatment; the findings on these parameters were similar in patients treated with oral naltrexone, which carries a boxed warning regarding hepatic effects. Mortality did not appear to be increased by Medisorb Naltrexone treatment, even in the opioid-dependent population, who are at risk for unintentional overdose when using illicit opioids during or after naltrexone treatment.

3.1 Exposure

The NDA included safety data from over 1000 exposed study participants, including sufficient long-term exposures for characterization of safety. In addition to the efficacy trial, ALK21-003, safety data were available from clinical pharmacology studies, open-label safety studies in alcoholics (including an extension of ALK21-003), and an open-label safety study in patients enrolling patients with opiate dependence, alcohol dependence, or both.

A table illustrating exposure by dose/duration is included in Dr. Kashoki's review as Table 7.2.1.3 on page 144.

In summary, the total exposure in all studies was as shown 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 |

This exposure included primarily subjects with alcohol dependence; however, ALK21-006 enrolled 121 outpatients with opiate dependence, 101 randomized to Medisorb Naltrexone 380 mg. By the time of the data cutoff date, 66 of the 101 patients had been administered at least 6 injections (≥ 6 months' exposure), and 11 had had at least 12 injections (≥ 12 months' exposure).

3.2 Deaths

A total of five deaths were reported in the Medisorb Naltrexone development program.

Causes of death included homicide (1), pancreatic cancer (1), suicide (2), and one unexplained death attributed by the medical examiner to complications of substance abuse.

All deaths occurred in patients on active drug. An association with study drug appears unlikely for all but the suicide deaths; in these cases, an association cannot be ruled out.

Both suicide deaths occurred in the context of long-term treatment with Medisorb Naltrexone (one patient's depressive episode developed after approximately 5 months of treatment, although suicide did not occur until two months after the last dose; one suicide occurred in an extension study after 33 doses of Medisorb Naltrexone).

3.3 Serious Adverse Events

In the controlled studies of 4-6 months' duration, 71 of 1090 (7%) subjects experienced SAEs. Of these, however, many of these experienced events which represented relapse to alcohol use, most frequently meeting criteria for seriousness because of inpatient treatment received. After removing the reports of alcohol-related SAEs from the analysis, Dr. Kashoki found that there were 47 patients who had an SAE. Psychiatric SAEs were most frequently reported. In particular, suicide-related SAEs occurred with greater frequency in the Medisorb Naltrexone 380-mg patients (1.4%) than in the placebo patients (0%). Serious injury was relatively infrequent (0.4% of all patients), and the risk of this SAE was similar across treatment groups. The risk of the other reported types of SAEs was either no higher or less for the active groups than the placebo group.

Other events of particular interest included an injection site reaction described as necrosis and requiring surgical resection, occurring in a subject shortly after receiving the first dose of Medisorb Naltrexone 380 mg.

In addition, a case of eosinophilic pneumonia and a case of interstitial pneumonia were reported in patients treated with Medisorb Naltrexone 380 mg.

In the 572 subjects observed for >6 months, 28 experienced an SAE after 6 months of treatment. Excluding 5 SAEs representing alcoholic relapse, 23 SAEs were reported. Events of particular interest included dehydration (2 subjects) and suicidal ideation (2

subjects). Dehydration occurred in the context of protracted emesis, possibly related to study drug, as nausea and vomiting are known effects of naltrexone.

Twenty-five additional SAEs were reported in the safety update, but no specific new safety concerns not noted in the previously-reviewed data were identified in these reports.

3.4 Discontinuations

Information relating to discontinuation of medication and discontinuation from study participation (sometimes occurring at different times for different stated reasons) was included in various parts of the case report form. In addition, an idiosyncratic approach to injection site reactions (ISRs) was employed, in which ISRs were assessed by the investigator as clinically significant or not clinically significant, and only clinically significant ISRs were reported as adverse events. Inexplicably, some patients discontinued study participation due to ISRs that were not coded as clinically significant and therefore not considered adverse events. A reanalysis of the reasons for discontinuation was required, taking into account all sources of information that could identify patients who ceased use of study medication for safety reasons.

Dr. Kashoki re-tabulated reasons for discontinuation using data captured in various CRF fields, and determined that:

Across the 4-6 month trials, slightly more patients (9.3%, 76/811) in the Medisorb Naltrexone groups withdrew due to an AE than patients in the placebo group (6.5%, 14/214). However, when rates of discontinuation were compared across specific dosage groups, the most discontinuations occurred in the 380-mg group (10.4%, 60/576), followed by the 400-mg group (8%, 2/25), and the 190-mg group (6.7%, 14/210). Patients treated with oral naltrexone were least likely to withdraw because of an AE (3.1%, 2/65).

The most common reason reasons for discontinuation among all patients were injection site reactions (2%), alcoholism (i.e. lack of treatment efficacy) (1%), nausea (0.9%), pregnancy (0.6%), abnormal LFTs (0.5%), and suicide-related AEs (0.4%). AEs associated with the 380-mg dose that led to more dropouts than in placebo group included injection site reactions (3% vs. 0.5%), nausea (2% vs. 0%), pregnancy (1% vs. 0%), headache (0.5% vs. 0%), and suicide-related AEs (0.3% vs. 0%)

Treatment with Medisorb Naltrexone appears to be associated with a slightly higher rate of dropouts due to suicidal behavior compared to treatment with placebo (0.9% vs. 0%, respectively). The risk of discontinuation due to this AE did not appear to be associated with increasing dose: 1% of patients in the 190-mg group vs. 0.4% of the 380-mg group and 0% of the 400-mg group.

The risk of dropout due to depression was also slightly greater in the combined Medisorb Naltrexone groups than in the placebo patients (0.25% vs. 0%). The

proportion of patients withdrawing due to depression was greatest in the oral naltrexone group (1.5%).

3.5 *Other Significant Adverse Events*

3.5.1 Hepatic Effects

Because this application was granted priority review status on the basis of the possibility that Medisorb Naltrexone represented a safety advantage over oral naltrexone with respect to hepatic effects, the Division gave particular attention to any evidence that Alkermes' product was superior to oral naltrexone in this regard. Alkermes' makes this assertion based on the following:

- Whereas the total monthly dose at which hepatotoxicity was observed with oral naltrexone (300 mg/day) would be 8400 mg, the total monthly dose of Medisorb Naltrexone is 380 mg (which is 22-fold lower than the total monthly dose of oral naltrexone).
- Administration of Medisorb Naltrexone suspension by gluteal IM injection avoids first-pass hepatic metabolism.
- Medisorb Naltrexone will be dispensed in single-dose kits and will be administered by a health care provider, reducing the risk of patient overdose.

Dr. Kashoki examined the laboratory values collected in the clinical trials, evaluating changes from baseline, considering both measures of central tendency and shifts from normal to abnormal (as well as abnormal to increasingly abnormal, important for this population with many abnormalities at baseline). She also examined the adverse event dataset for any events suggestive of hepatocellular injury. As expected in this alcohol-dependent population, GGT elevations were particularly common, and GGT improvements were noted in some groups.

Considering the data from the controlled studies (4-6 months' duration), Dr. Kashoki's review notes that "the data suggest that treatment with Medisorb Naltrexone only slightly increases mean LFT values by the end of treatment. The end-of-treatment mean LFT values are not much greater than those for the placebo group, suggesting no considerably increased risk of hepatocellular injury compared to placebo. Also, the mean LFT values suggest no difference in hepatic effect of Medisorb Naltrexone versus oral naltrexone." The shift tables revealed that higher proportions of patients in the Medisorb Naltrexone 380-mg group (14%) and the oral naltrexone group (10%) had a shift in ALT value from normal to the high limit of normal than did placebo patients (7%) or the 190-mg group (6%). Additionally, 3% of patients in the oral naltrexone group had a shift in AST from the high limit of normal to 3x the upper limit of normal, compared to 0% in the other groups. Otherwise, there no shifts from normal to abnormal in the active groups that were considerably different from the shifts observed in the placebo group.

Dr. Kashoki's review of the adverse event dataset for studies of 4-6 months' duration revealed that the frequency of hepatic-related AEs in the combined Medisorb Naltrexone subset was 4.6% (37/811). This was lower than the frequency in the placebo group (5.6%

(12/124)), and was comparable to the frequency in the oral naltrexone group (4.6% (3/65)). The risk of hepatic-related AEs did not appear to increase with increasing doses of Medisorb Naltrexone: 4.8% (10/210) of the 190-mg patients, 4.5% (26/576) of the 380-mg patients, and 4% (1/25) of the 400-mg patients. Consistent with the findings of the lab analysis, AE reports of LFT abnormalities (other than GGT, which is expected to decline with successful treatment and rise with exacerbation of alcohol drinking) were slightly more common among active-treated than placebo-treated patients (1.5% for 380 mg/400 mg vs 0.9% for placebo), but similar to the rate seen in patients treated with oral naltrexone (1.5%). In longer-term studies, approximately 6% of subjects treated with oral naltrexone, Medisorb Naltrexone 190 mg, or Medisorb Naltrexone 380 mg had LFT abnormalities reported as AEs.

One SAE of acute hepatitis was reported in a subject with a history of hepatitis C infection. The subject had completed six does of Medisorb Naltrexone 190 mg uneventfully, entered into the extension study, and completed an additional six does of treatment prior to developing acute hepatitis in the context of relapse to heavy drinking. The chronology does not suggest a role of Medisorb Naltrexone.

3.5.1.1 Post-marketing Hepatic Events Associated with Oral Naltrexone

The current ReVia label includes a boxed warning regarding the potential of naltrexone to cause hepatocellular injury when used in excessive doses. It does not appear that any serious hepatic events were part of the safety database that supported the labeling, and the use of a boxed warning in this circumstance may have been somewhat idiosyncratic.


Gita Akhavan-Toyserkani, Pharm D., of the Office of Drug Safety, examined the database of the Adverse Event Reporting System (AERS) to determine whether naltrexone has been associated with serious cases of liver injury.

Dr. Ahhavan-Toyserkani identified 29 cases, after excluding 25 additional cases based on the following:

- Information was insufficient (2)
- The primary event was not hepatotoxicity (4)
- The event was more likely to be attributed to another drug [Antabuse (3), Tylenol overdose (1)] or patient was not on oral naltrexone at the time of event (6)
- Diagnosis of viral hepatitis unlikely related to naltrexone (10)
- Pre-existing liver disease such as Wilson's disease (1)
- Pancreatic cancer metastasized to the liver and lymph nodes (1) and biliary obstruction (1)

The remaining 29 cases were reviewed and the reviewer noted:

The reported adverse events included increased hepatic enzymes, hepatitis, jaundice, cholestasis, fulminant liver failure and/or liver transplant. There were 4

cases of severe life-threatening injury with liver failure (Category 4); 4 cases of moderately severe to definitely life-threatening liver injury (Category 3B); 3 cases of moderately severe to possibly life-threatening liver injury (Category 3A) and 18 cases of mild (Category 1 or Category 2) liver injury.

The mechanism of liver injury from naltrexone use is not clear from the cases. We were not able to find a dose-response relationship in AERS cases. The majority of the cases that had dosages reported were receiving the recommended once daily 50mg dose (72%). The highest dose that was reported was 200-mg once daily. Although, the box warning states that ReVia does not appear to be a hepatotoxin at the recommended doses, the most frequently reported dose in the case series was the recommended 50mg once daily. Therefore, additional studies to more fully elucidate the hepatotoxic potential of naltrexone and its metabolites and any possible dose relationship may be necessary....

The majority of the cases were confounded with other contributory factors. However, a concurrent condition, does not exclude the possible contributory role of naltrexone, such as an additive effect. This case series supports a possible association between naltrexone and serious hepatic injury including hepatitis and liver failure. We recommend keeping the box warning in the current labeling at this time.

Therefore, it appears that the post-marketing safety experience with oral naltrexone supports the labeling already in place for ReVia. Although no cases of liver failure were noted during the clinical trial experience with Medisorb Naltrexone, it may be noted that none had been observed in association with ReVia at the time the label warning was added. The data in this application do not demonstrate a safety advantage of Medisorb Naltrexone over oral naltrexone with respect to effect on the liver. Although theoretical advantages were cited, when examining the laboratory data and the adverse event data, these advantages do not seem obvious. I do not believe the case has been convincingly made that this product provides a significant safety advantage over oral naltrexone.

3.5.2 Injection Site Reactions

Evaluation of injection site reactions in this database was complicated by the idiosyncratic handling of these events. Apparently, investigators were to assess ISRs and adjudicate them as “clinically significant” or “not clinically significant.” Only clinically significant ISRs were recorded on the adverse event forms. Therefore, there are two possibly analyses of ISRs—one using the ISR database, which captured all ISRs, and one using the adverse event database. The protocol did not provide guidance to investigators regarding the adjudication of clinical significance, and at least one subject is reported as having discontinued the study due to an ISR, which was adjudicated as not clinically significant despite its having led to premature study discontinuation. However, no matter what the approach to analysis, it was apparent that injection site reactions were common, and that the ISRs experienced by patients receiving active drug were of a more concerning and bothersome nature than those experienced by patients receiving placebo.

In the ISR database, injection site reactions (ISR) were common, with more than half of subjects reporting some type of ISR after at least one injection. When considering “all ISRs,” only a small difference was noted between placebo and active treatment, but placebo patients seemed to report primarily “injection site tenderness,” with few complaints of induration, pain, or pruritis. Tenderness was approximately as common among placebo-treated subjects as in active-treated. On the other hand, induration and pruritis were strikingly more common in subjects treated with the active injection compared to the matched-volume placebo for each dose. Induration was reported by 25-30% of active-treated patients, vs. 8-9% of placebo-treated. Pruritis was reported by 6% of active-treated patients and was not seen in placebo-treated patients. “Other” ISRs were reported by over 10% of active-treated patients, vs. 4% of placebo-treated. Injection site nodules and or lumps were the most common type of reaction labeled as “other.” Also predominant in this subset of ISRs was swelling at or around the site, discoloration, and rash. One patient had leakage of a considerable amount of study drug from the injection site.

“Clinically significant” ISRs occurred in 14% of subjects receiving active injections and only 6% of subjects receiving placebo injections. Furthermore, ISRs resulting in early termination of study participation occurred in less than 0.5% of placebo subjects, as compared to 2% of the 190 mg group, 3% of the 380 mg group and 4% of the 400 mg group. In addition, the duration of ISRs was longer in those who had received active injections than those who received placebo.

In the AE dataset, representing only those events sufficiently concerning that the investigator recorded them as adverse events, Dr. Kashoki found that “injection site pain” was the most frequently occurring ISR for all treatment groups, and was considerably more frequent in the high dose groups (~ 16%) than in the Medisorb Naltrexone 190-mg group (10%) and the placebo (7%) group.

Therefore, it appears that naltrexone itself, rather than the vehicle, excipients, or simply the volume of intramuscular injection has some local irritant effects. In addition, as noted above, one subject experienced an event described as “injection site necrosis” and required surgical resection of the injection site.

Alkermes examined the frequency of injection site reactions over time and found that fewer injections were followed by an ISR in later months of the study. This may be partially explained by the discontinuation of subjects who were prone to particularly troubling ISRs; however, as only 2-3% of subjects discontinued prematurely due to ISRs, this does not explain completely the finding. It does appear that as patients remain in treatment, ISRs become less of a problem over time. Nevertheless, ISRs are very common and often problematic for patients treated with Medisorb Naltrexone.

3.5.3 Psychiatric Events

Although depression is common among patients with substance abuse disorders and alcoholism is considered a risk factor for depression and suicide, the mechanism of action of naltrexone (antagonism at μ -opiate receptors, with potential to block action of

endogenous opioids) raises specific concerns about the product increasing the risk of dysphoria, depression, and possibly suicide above the background level in this population. The placebo-controlled studies allow for a comparison between groups with similar risk of depression and suicide which differ only in their exposure to naltrexone. Notably, suicidal ideation, suicide attempt, or any evidence of intentional self-harm did not occur in any patients treated with placebo. Although events of this type were uncommon (about 1% of active-treated subjects), their absence in the control group is suggestive of a drug effect. Events coded to terms such as “depression” or “depressed mood⁴” were twice as common in the 380 mg group than in the placebo group in Study ALK21-003, the 6 month placebo-controlled study (5% vs 10%).

In some cases, the suicidal thoughts/behavior occurred after study discontinuation, but were in the context of an episode of depression which began on study drug. Depression-related events associated with premature discontinuation of study drug were also more common in active-treated (~1%) than in placebo-treated patients (0).

These observations, along with the concerns raised by the mechanism of action of the drug, which could interfere with endogenous as well as exogenous opioids, suggest that naltrexone treatment is associated with an elevated risk of depressive symptoms, sometimes proceeding to suicidality. Appropriate labeling language alerting practitioners, patients, and patients families is warranted.

3.6 Events Suggestive of Allergic Response

A number of findings in Dr. Kashoki’s review suggest that patients may experience an allergic response to naltrexone. First, mean eosinophil counts rose in all treatment groups over the course of treatment, but this increase was higher in the Medisorb Naltrexone-treated than in the placebo-treated patients. In Study ALK21-003, the placebo group experienced a mean increase of 0.021 ($\times 10^3/\mu\text{l}$), vs. 0.065 for the Medisorb Naltrexone 190 mg group and 0.065 for the Medisorb Naltrexone 380 mg group. Second, the number of subjects with high eosinophil counts at week 24 showed the same pattern, with 1.4% of the placebo group, 2.4% of the Medisorb Naltrexone 190 mg group, and 6.3% of the Medisorb Naltrexone 380 mg group demonstrating elevated eosinophil counts. This observation is consistent with the pre-clinical findings as well.

In addition, cases of urticaria and angioedema, although reported infrequently (1.1% of all patients) were remarkable for the fact that all 12 cases occurred in Medisorb Naltrexone-treated patients.

Finally, three serious adverse events were reported that were suggestive of an allergic response: two cases of pneumonia (one coded as “interstitial pneumonia” and one as “eosinophilic pneumonia”), and the AE coded as “injection site necrosis,” described above, which included a pathology report that described the findings as consistent with a “hypersensitivity” reaction.

⁴ Terms included depression, major depression, worsening depression, increasing depression, depression exacerbation, moderate depression, and similar terms.

No cases of anaphylaxis were reported.

The Division of Pulmonary and Allergy Products was consulted, and the following comments were provided by Dr. Charles Lee:

Although it is not possible to rule out an IgE-mediated mechanism for these reactions, it is more likely that they are a result of non-IgE-mediated mast cell degranulation, as may be seen with iodinated radiocontrast media. IgE-mediated hypersensitivity is an immune mechanism, and sensitization is required before symptoms may occur from subsequent exposure. Two of the reactions occurred with the first dose, and one occurred just two days after drug administration, an insufficient period of time for the development of an immune response. Many of the patients had subsequent doses of drug without a recurrence of symptoms, which would be unusual for an IgE-mediated process. Appropriate treatment of urticaria or angioedema without associated respiratory or cardiovascular symptoms includes discontinuation of treatment and H1-receptor antagonists. If extensive or severe cutaneous involvement is present, H2-receptor antagonists and/or systemic corticosteroids may be used adjunctively.

Although it is more likely that urticaria and angioedema noted in the drug development program do not have an immune etiology, it is reasonable for the applicant to determine if the product elicits an immune response in humans. If positive in vivo or in vitro tests of drug specific antibody are found, it may be possible to assess if they may be predictive of these reactions. There may be some benefit in determining if naltrexone-specific, carboxymethylcellulose (CMC)-specific, or naltrexone/CMC-specific antibody is present in patients with these reactions. Percutaneous skin testing or in vitro tests drug-specific IgE may of benefit in determining if there is an IgE-mediated process. In vitro tests of drug-specific IgM, or IgG may be helpful in determining if a Type III or immune complex-mediated reaction is present. Delayed hypersensitivity skin testing or patch testing may be of benefit in determining if a Type IV or delayed hypersensitivity reaction is involved.

As noted earlier, eosinophilia may be associated with IgE-mediated conditions, such as asthma with allergic triggers, but its presence is not diagnostic for an allergic process. It is also unclear if the mechanism for the eosinophilia and the eosinophilic pneumonias is the same, and it is unclear if an immunologic process is involved. In the absence of evidence for a specific immunologic etiology, it is not possible to determine if in vitro or in vivo testing could predict the development of eosinophilia or eosinophilic pneumonia and impossible to determine if similar reactions could be prevented.

Long-term follow-up in study ALK21-003-EXT suggested that patients with eosinophilia had normalization of their eosinophil counts by Week 40. These data suggest that no treatment is necessary for patients that develop eosinophilia with

Medisorb Naltrexone treatment. If eosinophilia is detected in these patients, it would be reasonable to follow eosinophil counts until they normalize.

Patients developing eosinophilic pneumonia should have the drug discontinued. As with the two patients who developed eosinophilic pneumonias, treatment with systemic corticosteroids may be indicated once infection has been excluded.

Dr. Lee also commented that a trial or run-in period with oral naltrexone would be of little benefit, as these reactions were not seen with oral naltrexone and may be related specifically to the Medisorb Naltrexone formulation.

A search of the AERS database for terms related to allergy or eosinophilia revealed 15 cases. The most common event reported was “face oedema” (5 cases); two additional cases report “hypersensitivity” without additional information. The most serious cases included some which could not be clearly linked to naltrexone: a case of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (in duplicate reports) occurred in the setting of multiple concomitant medications. In addition, a case of pneumonia was reported; in this case, the patient developed aspiration pneumonia as a complication of anesthesia-assisted detoxification. Of the events which are serious and seem attributable to naltrexone, there was one case described as “extensive erythema multiforme” and one case of anaphylaxis.

In further consultation with the Division of Pulmonary and Allergy Products, Drs. Badrul Chowdhury, Division Director, and Lydia Gilbert-McClain, Deputy Director, indicated that idiopathic eosinophilic pneumonia is a very concerning event which is life-threatening if untreated. Although drug-induced eosinophilic pneumonia is a recognized entity, and usually less severe than idiopathic acute eosinophilic pneumonia, more severe cases have recently been reported in association with drug use. In the cases reported in the Medisorb Naltrexone safety database, the degree of severity warrants a high level of concern.

3.7 Common Adverse Events

Dr. Kashoki pooled data from ALK21-002 and ALK21-003, which were most similar in duration, design, and population, to explore the incidence of common drug-related adverse events. For some terms of interest, Higher Level Terms (HLT) were employed to combine related Preferred Terms. Dr. Kashoki found that gastrointestinal-related AEs were the most commonly-reported type of AE. Gastrointestinal events reported more commonly in Medisorb Naltrexone patients than placebo patients included nausea (29% vs. 11%), vomiting (12% vs. 6%), diarrhea (13% vs. 10%), abdominal pain (12% vs. 8%), dry mouth (6% vs. 4%), and flatulence/bloating (2% vs. 0.9%). In general, these AEs were more frequent at the higher doses (380- and 400-mg). Additionally, a greater number of patients in the Medisorb Naltrexone group than in the placebo group experienced a decrease in appetite (11% vs. 3%) and in weight (1.4% vs. 0.5%)

Other events reported more commonly among active-treated patients than placebo-treated included asthenia (e.g. fatigue, malaise, lethargy) (20% vs. 12%), injection site reactions were considerably more frequent in the Medisorb Naltrexone group than the placebo group (25% vs. 8%), headache (21% vs. 18%), dizziness (13% vs. 4%), somnolence/sedation (5% vs. 1%), muscle cramps (5% vs. 1%), arthralgia (8% vs. 5%) and back pain (6% vs. 5%).

Also, more patients treated with Medisorb Naltrexone reported rash (6% vs. 4%) and angioedema/urticaria (2% vs. 0%)

Treatment with Medisorb Naltrexone appeared to confer a slightly increased risk of psychiatric effects, including anxiety (10% of Medisorb Naltrexone-treated patients vs 8% of placebo-treated) depression and/or suicidal ideation (6% of Medisorb Naltrexone-treated patients vs 4% of placebo-treated).

As noted above, the data showed a slightly greater proportion of patients in the Medisorb Naltrexone group had increases in AST compared to the placebo group (1.6% vs. 0.9%). However, overall, treatment with Medisorb Naltrexone was *not* associated with more frequent increases in liver function tests (AST, ALT, GGT, or bilirubin) compared to placebo (6% vs. 7%).

The table below was prepared primarily by Dr. Kashoki using the sponsor's adverse event datasets. She combined terms as indicated in the table to yield more meaningful incidence rates. I elected to replace the data on injection site reactions, taken from the AE dataset, with data from the ISR dataset, because of the poorly-explained discrepancy between the high rate of ISRs reported in the ISR dataset and the much lower rate included in the AE dataset. I believe that the "non-clinically significant" ISRs should also be reflected in the AE table shown in labeling, to give a realistic expectation to clinicians and patients regarding the likelihood of experiencing an injection-site reaction of any type.

Common Adverse Events (by body system and preferred term/high level group term) in $\geq 5\%$ of patients treated with VIVITROL

| Body system/SOC | Adverse Event/Preferred Term | Placebo | | Medisorb Naltrexone | | | | | | | |
|--|--|---------|----|---------------------|----|-------------------|----|-------------------|----|----------------|-----|
| | | N = 214 | | 400-mg N = 25 | | 380 mg N = 205 | | 190 mg N = 210 | | All N = 440 | |
| | | N | % | N | % | N | % | N | % | N | % |
| Gastrointestinal disorders | Nausea | 24 | 11 | 8 | 32 | 68 | 33 | 53 | 25 | 129 | 29 |
| | Vomiting NOS | 12 | 6 | 3 | 12 | 28 | 14 | 22 | 10 | 53 | 12 |
| | Diarrhea ¹ | 21 | 10 | 3 | 12 | 27 | 13 | 27 | 13 | 57 | 13 |
| | Abdominal pain ² | 17 | 8 | 4 | 16 | 23 | 11 | 23 | 11 | 50 | 11 |
| | Dry mouth | 9 | 4 | 6 | 24 | 10 | 5 | 8 | 4 | 24 | 5 |
| | Abnormal liver function test - Total | 14 | 7 | 3 | 12 | 12 | 6 | 12 | 6 | 27 | 6 |
| | Upper respiratory tract infection - Other ³ | 28 | 13 | 0 | 0 | 27 | 13 | 25 | 12 | 52 | 12 |
| Psychiatric disorders | Pharyngitis ⁴ | 23 | 11 | 0 | 0 | 22 | 11 | 35 | 17 | 57 | 13 |
| | Insomnia, sleep disorder | 25 | 12 | 2 | 8 | 29 | 14 | 27 | 13 | 58 | 13 |
| | Anxiety ⁵ | 17 | 8 | 2 | 8 | 24 | 12 | 16 | 8 | 42 | 10 |
| | Depression & suicidal ideation combined | 9 | 4 | 0 | 0 | 17 | 8 | 9 | 4 | 26 | 6 |
| | Depression only | 9 | 4 | 0 | 0 | 17 | 8 | 7 | 3 | 24 | 5 |
| | Suicidal ideation only | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 2 | 0.5 |
| | Any ISR | 106 | 50 | 22 | 88 | 142 | 69 | 121 | 58 | 285 | 65 |
| General disorders and administration site conditions | 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 ⁶ | 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 Eczthymosis | 11 | 5 | 0 | 0 | 14 | 7 | 9 | 4 | 23 | 5 |
| | Asthenic conditions ⁷ | 26 | 12 | 3 | 12 | 47 | 23 | 40 | 19 | 90 | 20 |

¹ Includes the preferred terms: diarrhea NOS; frequent bowel movements; gastrointestinal upset; loose stools

² Includes the preferred terms: abdominal pain NOS; abdominal pain upper; stomach discomfort; abdominal pain lower

³ Includes the preferred terms: upper respiratory tract infection NOS; laryngitis NOS; sinusitis NOS

⁴ Includes the preferred terms: nasopharyngitis; pharyngitis streptococcal; pharyngitis NOS

⁵ Includes the preferred terms: anxiety aggravated; agitation; obsessive compulsive disorder; panic attack; nervousness; post-traumatic stress

⁶ Primarily nodules, swelling

⁷ Includes the preferred terms: malaise, fatigue (these two comprise the majority of cases); lethargy; sluggishness

| Body system/SOC | Adverse Event | Placebo N = 214 | | Medisorb Naltrexone | | | | | | | |
|---|---|--------------------|----|---------------------|----|-------------------|----|-------------------|----|----------------|----|
| | | | | 400-mg N = 25 | | 380 mg N = 205 | | 190 mg N = 210 | | All N = 440 | |
| | | N | % | N | % | N | % | N | % | N | % |
| Musculoskeletal and connective tissue disorders | Arthralgia, arthritis, joint stiffness | 11 | 5 | 1 | 4 | 24 | 12 | 12 | 6 | 37 | 9 |
| | Back pain, stiffness ⁸ | 10 | 5 | 1 | 4 | 12 | 6 | 14 | 7 | 27 | 6 |
| | Muscle cramps ⁸ | 3 | 1 | 0 | 0 | 16 | 8 | 5 | 2 | 21 | 5 |
| Skin and subcutaneous tissue disorders | Rash ⁹ | 8 | 4 | 3 | 12 | 12 | 6 | 10 | 5 | 25 | 6 |
| | Headache ¹⁰ | 39 | 18 | 9 | 36 | 51 | 25 | 34 | 16 | 94 | 21 |
| Nervous system disorders | Dizziness, syncope | 9 | 4 | 4 | 16 | 27 | 13 | 27 | 13 | 58 | 13 |
| | Somnolence, sedation | 2 | 1 | 3 | 12 | 8 | 4 | 9 | 4 | 20 | 5 |
| Metabolism and nutrition disorders | Anorexia, appetite decreased NOS, appetite disorder NOS | 6 | 3 | 5 | 20 | 30 | 14 | 13 | 6 | 48 | 11 |

⁸Includes the preferred terms: muscle cramps, spasms, tightness, twitching, stiffness, rigidity

⁹Includes the preferred terms: rash NOS, rash papular, heat rash

¹⁰Includes the preferred terms: headache NOS, sinus headache, migraine, frequent headaches

3.8 Laboratory Data

Effects on hepatic enzymes and eosinophil count were discussed above. Other than that, the only notable findings in the laboratory data were a slight decrease in platelet count among the subjects treated with Medisorb Naltrexone 380 mg and a slight increase in CPK (seen in all groups, including oral naltrexone; therefore not explained by intramuscular injections).

3.9 Vital Signs, Weight

No consistent effect of naltrexone on vital signs or weight was identified.

3.10 Off-Label Safety in Opiate Abusing Population

Opioid-addicted patients are particularly vulnerable to overdose following detoxification. Their level of tolerance to opioids is significantly reduced from the pre-detoxification level, and in this setting, inadvertent overdose can occur when the patient relapses to illicit drug use. Patients treated with naltrexone are protected against the effects of overdose while the naltrexone blockade persists. However, some may attempt to override the blockade by taking larger and larger doses of opioids. Because of the uncertainty of the duration of blockade, it may be possible for a patient to tolerate a particular dose of opioid, and then gradually lose tolerance as the blockade wanes. This raises the possibility of accidental overdose in patients treated with naltrexone. Those treated with oral naltrexone can simply stop taking the drug; within several days, the effects of naltrexone are no longer present. Those treated with a depot formulation, however, experience a longer period of changing plasma levels and receptor blockade levels. Alkermes was asked to evaluate the safety of Medisorb Naltrexone in patients who might relapse to illicit opioid use.

Study ALK21-006 was a one-year, open-label study comparing Medisorb Naltrexone 380 mg to oral naltrexone, which randomized 101 subjects with either opiate dependence or mixed alcohol/opiate dependence to treatment with Medisorb Naltrexone and 20 such patients to oral naltrexone. Three cases of heroin overdose were observed, two in the Medisorb Naltrexone-treated patients and one in the oral naltrexone-treated patients. No case was fatal. All the events occurred well after the last dose of study drug (53 days for the oral naltrexone case; 60 days and 75 days after the last injection for the Medisorb Naltrexone cases). The data, although limited, do not suggest that depot naltrexone is more hazardous to this population than the already-approved oral formulation.

4 DISCUSSION OF SAFETY AND EFFICACY ISSUES

The efficacy data supporting this application was limited to a single efficacy study. The primary analysis demonstrated that the group treated with Medisorb Naltrexone 380 mg reduced their heavy drinking days more than the placebo-treated patients. Although this analysis was one of several suggested by the Agency during the design of the trial, ultimately, the clinical significance of the degree of reduction seen was uncertain.

Exploratory analyses aimed at identifying responses at the individual level which drove the group response revealed that very few of the study participants were able to achieve a sustained pattern of non-risky drinking behavior, and the study drug did not appear to have an effect on increasing the likelihood of achieving this response. Only in the subset of patients abstinent at baseline was an effect apparent. Notably, the original approval of oral naltrexone was based on studies in patients abstinent at baseline, although the labeling does not restrict the use of the product to this population. Nevertheless, there appears to be insufficient evidence of efficacy in patients drinking actively at baseline

In fact, even the primary analysis, "event rate of heavy drinking," does not show a statistically-significant effect of naltrexone in subjects who were drinking at treatment initiation, which represents the vast majority of enrolled subjects.

Furthermore, DSI inspection of three study sites for the efficacy study revealed protocol violations regarding the collection of the efficacy data at two of three sites. At these sites, some of the TLFB interviews were conducted by the same person who provided the psychosocial therapy. It is generally accepted that collection of efficacy data by the therapist may increase the likelihood of patients minimizing their reports of drinking. Had *all* efficacy data at *all* sites been collected by a therapist, one could conclude that the drinking data may have been overly-optimistic, but that the treatments would have no differential effect on truthfulness, allowing for comparisons between treatments.

5 PRE-CLINICAL ISSUES

Pre-clinical evaluation of the Medisorb Naltrexone formulation was limited. The applicant intended to rely upon previous agency findings of safety for the oral formulation of the active moiety (referencing NDA 18-932 and providing appropriate paragraph II patent certifications), but also hoped to make reference to other findings concerning the polylactide-co-glycolide microspheres, which have been used in other products. Questions have arisen concerning whether or not it is appropriate to incorporate these agency findings in support of this application. Moreover, the pharmacology/toxicology review team has also concluded that aspects of the active ingredient's interactions with its polymer matrix may render studies of the polymer in other drug products inapplicable to the safety of this specific product. Therefore, even if all referenced findings could be incorporated into the decision, some information regarding the preclinical safety of Medisorb Naltrexone remains unavailable. In particular, Dr. R. Daniel Mellon, supervisory pharmacology/toxicology reviewer, has concluded that there is insufficient information about reproductive, genetic, and carcinogenic potential of Medisorb Naltrexone to support approval.

6 CHEMISTRY, MANUFACTURING, AND CONTROLS ISSUES

The proposed product is a kit, consisting of a single-use vial of naltrexone-PLG microspheres, a vial of sterile, aqueous diluent, and a dedicated syringe and needles packaged in a thermoform tray. Review of the chemistry, manufacturing, and controls section of the application was conducted by Dr. Jila Boal under the supervision of Dr. Ravi Harapanhalli. The most problematic aspect of the review was the relative lack of

data on the scaled-up batch size; however, this was resolved with a shortened expiry period. The microbiology review identified no sterility concerns.

Naltrexone, like other opiates, contains an _____ impurity considered to be a structural alert for mutagenic potential. The level of _____ impurity will be controlled in the drug substance by the supplier _____. An interim release specification of _____ has been established, which will then be followed by a final release specification of _____ ppm after March 2007. Alkermes will establish a specification for impurities in the drug substance naltrexone base anhydrous once changes are made to _____ Drug Master File (DMF).

The data show that the rate and amount of drug release both increase with increasing temperatures (e.g. $\geq 40^{\circ}\text{C}$). Thus, there is the potential for rapid drug release and increased exposure in patients with elevated temperatures, e.g. during a fever.

The data also showed that, on average, about 30% of naltrexone is released during the first 7-10 days. This corresponds to release of approximately 114 mg of naltrexone in the initial 1-2 weeks. The variation in drug release / dissolution specifically at day 7 could partially be due to the _____

_____ hereby affecting the day 7 to day 14 dissolution rates. The Applicant proposes an upper limit drug release specification of about _____. This means that there is the potential for release of approximately _____ mg of naltrexone in the first 2 weeks. Because of safety concerns related to this rapid release of drug, the Applicant is being asked to revise the specifications following accrual of additional manufacturing experience from five consecutive commercial batches.

7 CLINICAL PHARMACOLOGY ISSUES

The clinical pharmacology and biopharmaceutics review was conducted by Dr. Srikanth Nallani. Dr. Nallani noted that, although one putative safety advantage of Medisorb Naltrexone over oral naltrexone was a lower total monthly dose, the total exposure to naltrexone is actually higher from Medisorb Naltrexone than from oral naltrexone:

The proposed dose of Medisorb Naltrexone is 380 mg over 28 days. The total dose of oral naltrexone (50 mg/day) over that same time period would be 1400 mg. Thus the total dose IM Medisorb Naltrexone is approximately one third of the oral naltrexone dose. However, the *exposure* to naltrexone (AUC_{0-28}) over 28 days following a single Medisorb Naltrexone dose is approximately four-fold higher than that observed with oral naltrexone. This appears to be a result of bypassing of first pass metabolism by the administering drug via the IM route.

In addition, as would be expected, the exposure to the active metabolite, 6β -naltrexol, is reduced.

Dr. Nallani identified concerns regarding the methodology used in the Applicant's *in vitro* cytochrome P450 inhibition studies, and will be requesting that the Applicant repeat these studies using an accepted method.