IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Elliot Ehrich		
Application No.	11/083,167	Group No.	1617
Filed:	March 17, 2005	Examiner:	Kendra D. Carter
Confirmation No.	8002		
For:	Naltrexone Long Acting Formulations and Methods for Use		

DECLARATION UNDER 37 CFR 1.132

Dear Sir:

I, Elliot Ehrich, am the inventor of the subject matter of the above-identified application. I am also employed by Alkermes, Inc, the assignee of the above-identified application. My curriculum vitae is attached hereto as Exhibit D.

Background

The present invention is directed to the unexpected discovery that a single injection of a naltrexone-containing long-acting formulation provides systemic exposure to naltrexone (AUC) which is at least 2 fold higher over a 28 day period than the AUC of an oral regimen of 50 mg per day over a 28 day period. The invention which is described in the above identified application resulted from a discovery made during clinical trial testing of Alkermes' MEDISORB® (injectable) Naltrexone (tradename VIVITREX®). Due to the size of the lengthy full Clinical Study Report only relevant portions of the Clinical Study Report # ALK21-005 (the "Report") finalized November 9, 2004 is attached hereto as Exhibits A and B. I will be referring to this Report throughout my declaration.

Prior to obtaining the data discussed in the Report, it was believed that the doses of MEDISORB® Naltrexone suspension selected for the studies described in the Report (i.e. 190 mg and 380 mg) would result in total systemic exposure (AUC) which was similar to the AUC of an oral regimen of 50 mg per day naltrexone over a 28-day period. However,

as the data summarized in Table 8 of Exhibit A shows, the 380 mg dose has an AUC that is at least 3.3 times greater than the AUC of the per day dose of oral regimen of 50 mg per day naltrexone.

Data Analysis

Referring now to Table 8 of the Report shown in Exhibit A, note that the AUC_{0-t} ($AUC_{0-28days}$) for a single dose of MEDISORB® Naltrexone 380 mg on a per day basis can be calculated for Cohort A by dividing the AUC_{0-t} for Cohort A 120.6 by 28 days and for Cohort B, 137.8, by 28 days. For Cohort A, the per day 380 mg MEDISORB® Naltrexone AUC_{0-t} is 4.307 which is about 3.3 times greater than the per day AUC_{0-t} of oral Naltrexone 50 mg which is 1.278. For Cohort B, the per day 380 mg MEDISORB® Naltrexone AUC_{0-t} is 4.921 which is about 3.3 times greater than the per day AUC_{0-t} of oral Naltrexone 50 mg which is 1.468. This result was unexpected.

Based on the dose proportionality observed between 190 and 380 mg following a single dose, $AUC_{0-28days}$ for the 190 mg dose may reasonably be predicted to be approximately 2-fold higher than AUC following oral dosing of 50 mg per day for 28 days. This is also evident from Cohort A data showing about a 2-fold higher AUC for MEDISORB® Naltrexone 190 mg. This result was also unexpected.

Cited Reference US Pat No 6,306,425 ("Tice")

I have read the rejections from the Examiner and I have reviewed Tice cited by the Examiner. The Examiner claims that the data found in the table in column 14 of Tice indicates that the F-1' naltrexone-containing injectable formula described also exhibits an AUC which is 3.3 times higher over a period of 32 days as compared to the oral dosing of 50 mg per day of naltrexone for 32 days. This is incorrect.

Tice discloses an injectable formulation containing up to 350 mg of naltrexone. However, Tice does not disclose that the serum AUC of naltrexone is at least about 2 or 3.3 times greater than that achieved by the equivalent 50 mg/day oral administration over

the same period of time. Given that the oral naltrexone is delivered in a daily dose, it is necessary to either extrapolate (or actually measure) the AUC derived from the daily oral dose over the time period in which the AUC of the injectable extended dose is measured, or it is necessary to divide the AUC of the injectable extended dose over the number of days that AUC measurements of the injected extended dose are taken in order to arrive at the daily AUC of the extended dose and thereafter compare that measurement to the daily AUC of the daily oral dose. Therefore what is actually disclosed Tice is that the *extrapolated* 32 day AUC after a single dose of a 50 mg tablet of oral naltrexone (column 15, lines 62-65, 1600 mg naltrexone total dose) is similar to the AUC_{0-32} day after injection of the F-1' naltrexone formulation tested in Tice.

The table in column 15 summarizes the data table in column 14 of Tice which compares the dose delivered in one day (with 50 mg) as compared to the delivery over 32 days. The mean dose is calculated by multiplying the mean daily dose over 32 days (to calculate the dose/day) is 27.8*32=889.6. The F-1' mean over 32 days achieved a 1051.6, which is less than twice the AUC. Looking at the data differently, the AUC over 32 days is 1051.6. The dose per day is 32.8 (1051.6/32 = 32.8), which is not twice 27.8, the per day dose for the 50 mg oral.

Comparison between Tice and the Present Application

Referring now to the graphs of Exhibit C, AUC data for Tice are taken from the text and table in column 14. According to the table, a single oral dose of 50 mg naltrexone was administered, and a mean AUC_{0-24h} value of 27.8 *ug* h/L was obtained. This value is presented in the graph of Exhibit C as the average daily AUC level for each of 32 days. A second set of data indicates that a single 300 mg injection of naltrexone resulted in a mean AUC_{0-32d} value of 1051.6 *ug* h/L. This value was divided by 32 days, and then graphed in Exhibit C as the average daily AUC value of 32.9 *ug* h/L.

AUC data for MEDISORB® Naltrexone are taken from the text and table on page 6 of their clinical study report ALK21-005 (Exhibit B). According to the table on page 6 of

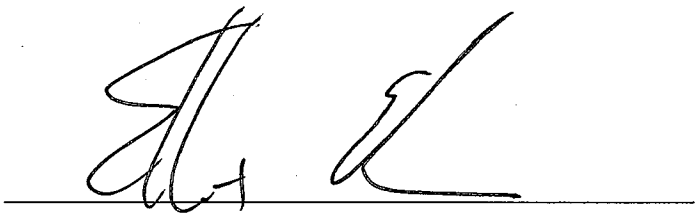
the Report, a single oral dose of 50 mg naltrexone was administered, and a mean $AUC_{0-\infty}$ value of 30.5 *ug* h/L (1.270 ng days/mL) was obtained. This value is presented in the graph of Exhibit C as the average daily AUC level for each of 32 days. A second set of data indicates that a single 190 mg injection of naltrexone resulted in a mean $AUC_{0-\infty}$ value of 1722 *ug* h/L (71.75 ng days/mL). This value was divided by 32 days, and then graphed in Exhibit C as the average daily AUC value of 53.8 *ug* h/L. A third set of data indicates that a single 380 mg injection of naltrexone resulted in a mean $AUC_{0-\infty}$ value of 3444 *ug* h/L (143.5 ng days/mL). This value was divided by 32 days, and then graphed in Exhibit C as the average daily AUC value of 107.6 *ug* h/L.

Comparisons between the graphed data from column 14 of Tice and the data from Exhibit B as shown in Exhibit C indicate that the 50 mg oral doses of Tice and Exhibit B and the single injectable dose of 300 mg of Tice result in similar average daily AUC values of 28-33 *ug* h/L. On the other hand, a single injectable dose of MEDISORB® Naltrexone 190 mg or MEDISORB® Naltrexone 380 mg (Alkermes) result in average daily AUC values that are, respectively, 1.6x (53.8 *ug* h/L) and 3.3x (107.6 *ug* h/L) greater than the average daily AUC value of 32.9 *ug* h/L, obtained from a single injectable dose of 300 mg in accordance with Tice.

Conclusion

Therefore, Tice does not disclose an injectable naltrexone formulation that has the presently claimed AUC of at least 3.3 times greater than that of 50 mg oral Naltrexone. In addition, based on what was known in the prior art including Tice, it was unexpected that an injectable naltrexone formulation such as the MEDISORB® Naltrexone formulation would have an AUC of at least 3.3 times greater than that of 50 mg oral Naltrexone.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Elliot Ehrich

Attachments: Exhibits A, B, C and D

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.