**PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | |
|---|---|---|
| In re Application | ) | Confirmation No.: |
| Inventor: Gregory T. Went, et al. | ) | Art Unit: 1627 |
| Application No.: | ) | Examiner: Kendra D. Carter |
| Filed: June 25, 2012 | ) | Attorney Docket No. 34550-718.305 |
| Title: Method for Administering an NMDA Receptor Antagonist to a Subject | ) | |

**Declaration Under 37 C.F.R. § 1.132**

I, Gregory T. Went, Ph.D., declare as follows:

1. I am an inventor of the patent application identified above ("Application"), and the subject matter described and claimed therein.

2. I am Co-founder, and am currently the Chief Executive Officer, of Adamas Pharmaceuticals, Inc., the assignee of the Application.

3. My curriculum vitae is attached as Appendix A.

**Memantine Property Background – Half Lifeand Side Effects**

4. Extended-release products are usually designed to prolong the absorption of drugs with short half-lives, thereby allowing longer dosing intervals, while minimizing fluctuations in serum drug levels. (Remington's: The Science and Practice of Pharmacy, 21st Ed., pp. 944-45 (2006)).

Memantine is a long half-life drug (about 60 hours), which is nearly completely bioavailable when given in immediate release form (Namenda package insert (2011)), and at the time the invention was made, was approved for dosing twice daily. This means that once immediate release memantine is given, its blood plasma concentration rises over a period of about 0-7 hours and then starts to slowly decrease. The blood plasma concentration has generally not decreased significantly before the next dose of memantine is given after 12 hours.

A person having ordinary skill in the art at the time of filing of the Application would have lacked motivation to prepare an extended release form of memantine to extend its duration of activity, as duration of activity is not really an issue with memantine. Nor would that person have been motivated to develop and administer memantine formulations with a specific initial rate of increase in concentration, with an expectation of success in significantly reducing memantine's CNS side effects to the point where it could be administered once per day, alone or with donepezil.

6. Extended-release formulations may also be useful to reduce the peak plasma concentrations of drugs for which high peak plasma concentrations are associated with significant adverse effects in certain situations. However, the most significant side effects of immediate release memantine are actually observed early in memantine dosing (Ambrozi, Pharmacopsychiat., 21(3): 144-146 (1988); Ditzler, Drug Res. 41(11), Nr. 8: 773-780 (1991)), when plasma concentrations are a fraction of steady state peak plasma concentration. Thus, the person of ordinary skill in the art would not have been motivated to prepare an extended release form of memantine to lower its peak plasma concentrations, as the most serious side effects of memantine appear before memantine has achieved high plasma concentrations.

7. Immediate release memantine is not well tolerated at doses higher than the labeled dose (i.e. above 20 mg/day) (Maier et al., Pain 103: 277-283 (2003); Swerdlow, Neuropsychopharm. 34:1854-1864 (2009)). While reducing Cmax sometimes may be considered a reasonable basis for developing extended release formulations of short half-life drugs, given the already relatively low fluctuation of plasma memantine concentration observed with immediate release memantine at steady state (owing to the significant accumulation of the drug at steady state due to its long half life), extending the release of memantine would not have been expected to significantly reduce the Cmax at steady state. Thus, a person of ordinary skill in the art would not have expected that extending the release of memantine would improve its tolerability at doses higher than the label doses (*i.e.*, greater than 20 mg per day.) A person having ordinary skill in the art at the time of the filing of the Application would therefore have lacked motivation to formulate an extended release formulation of memantine, dosed once daily, at strengths greater than 20 mg/day (more specifically from 22.5 mg to 30 mg.) Without such motivation, the person of ordinary skill in the art would not have found it obvious to formulate a

once-a-day extended release formulation of 22.5 mg to 30 mg of memantine.

**Experiments Conducted**

ADS-DEM-C106: Pharmacokinetic Characterization of Memantine Immediate Release (IR), and Memantine Extended Release (ER) Forms A, B and C

8. A cohort of 64 subjects was randomized to one of four treatment arms of 16 subjects each – IR, A, B and C. Treatment arm IR received a single dose of 20 mg of a commercially available immediate release memantine (Namenda®). Treatment arm A received 22.5 mg of a first extended release memantine formulation. Treatment arms B and C received 22.5 mg of memantine in second and third ER formulations of memantine, respectively. Blood was drawn at T=0 and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 36, 48, 96, 144, and 192 hours after oral administration of memantine for each treatment arm, for the determination of memantine blood plasma level at each time point. Results of this study are depicted graphically in Figures 1a and 1b, below. (Figure 1a depicts the line representing 50% IR dC/dT over 0-Tmax; Figure 1b depicts the line representing a dC/dT of 50% of memantine IR over 0-6 hours.)

**Figure 1a. Results from ADS-DEM-C106 Plasma Memantine Concentration Profile per Mg of Memantine (with the line for dC/dT of 50% of memantine IR running from 0 to Tmax)**

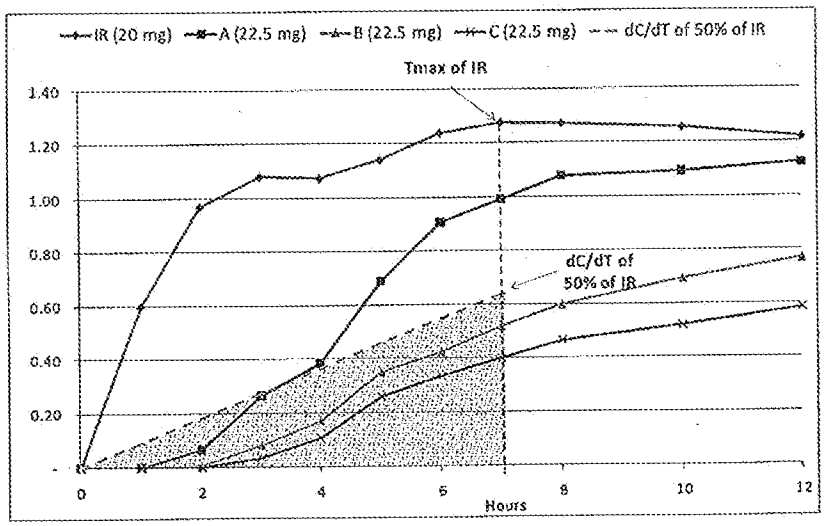
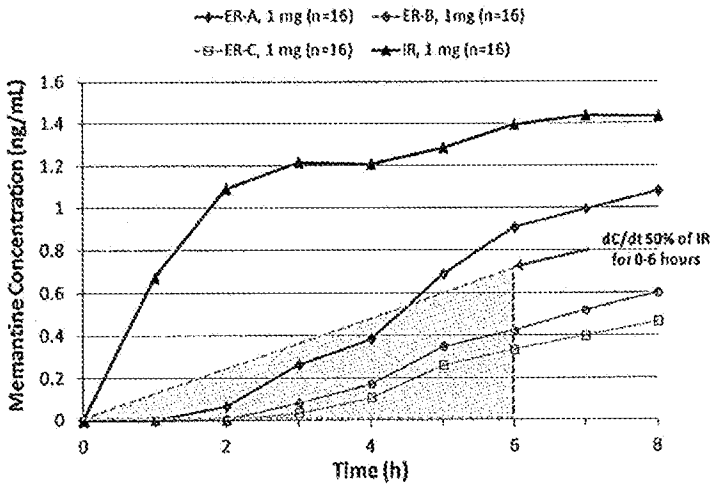


**Figure 1b. Results from ADS-DEM-C106 Plasma Memantine Concentration Profile per Mg of Memantine (with the line for dC/dT of 50% of memantine IR running from 0-6 hours)**




9. Results of ADS-DEM-C106: As can be seen in Figures 1a and 1b, above:

- The IR memantine formulation achieved maximum blood plasma concentration in about 7 hours, in agreement with the literature (Namenda Package Insert) corresponding to a rate of change of memantine blood plasma concentration (i.e., dC/dT) of about 4 ng/ml/hr;
- ER memantine formulation A achieved 80% of the IR dC/dT over 0-Tmax; similarly, formulation A achieved a dC/dT as measured between the period of 0-6 hours of the IR formulation of about 73% of the IR formulation (adjusted proportionally for strength);
- ER memantine formulation B achieved 40% of the IR dC/dT over 0-Tmax; similarly, formulation B achieved a dC/dT as measured between the period of 0-6 of the IR formulation of about 34% of the IR formulation (adjusted proportionally for strength);
- ER memantine formulation C achieved 30% of the IR dC/dT over 0-Tmax; similarly, formulation C achieved a dC/dT as measured between the period of 0-6 hours of the IR formulation of about 27% of the IR formulation (adjusted proportionally for strength) .

Thus, whether measured over 0-6 hours or 0-Tmax, two of the tested ER formulations (B and C) fall within the initial dC/dT requirement specified in the application and the subject of the pending claims, whereas the IR and formulation A ER memantine formulations do not.

10. In addition to the relative dC/dT, the absolute rate of increase in memantine for formulations B and C (falling within the instant claim) were calculated from the mean plasma concentrations from 2 to 4 hours. The values are reported in Table 1 below and are shown graphically in Figure 2. For ER memantine formulation B, the concentration increased steadily, after an initial lag of 2 hours, over 8 hours post dosing. The absolute rate of initial increase in concentration within the first 4 hours of the profile from 2 hours to about 4 hours post dose is about 1.9 ng/mL/hour. For ER memantine formulation C, the concentration increased steadily, after an initial lag of 2 hours, over 8 hours post dosing. The absolute rate of initial increase in concentration within the first 4 hours of the profile from hour 2 to about 4 hours post dose is about 1.2 ng/mL/hour. Thus, the ER profiles with an absolute rate of increase in initial concentration less than 2.1 ng/ml/hr are well-tolerated.

**Figure 2. Results from ADS-DEM-C106 Plasma Memantine Concentration Profile**

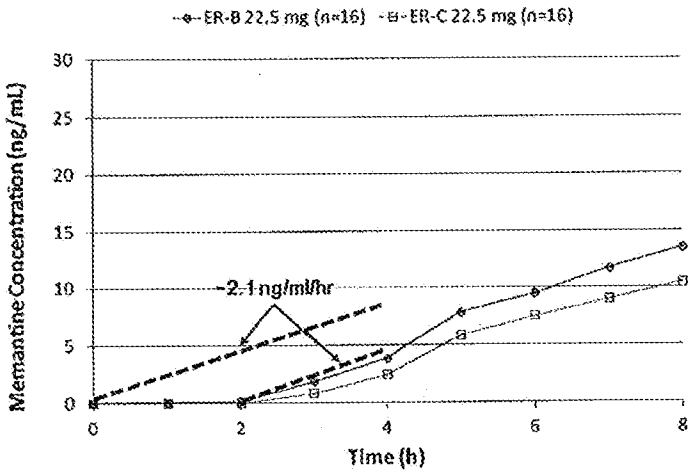



**Table 1. Absolute dC/dT within 2-4 hours**

| Formulation | Dose (mg) | Duration t1-t2 hour | Slope (ng/mL/hour) |
|---|---|---|---|
| B | 22.5 | 2-4 | 1.9 |
| C | 22.5 | 2-4 | 1.2 |

11. Reduction in CNS Side Effects: The subjects in the study were evaluated for side

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.