IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	11/399,879	**Customer No.:**	94584
Applicant:	Went et al.	**New Docket No.:**	34550-705.501
Filed:	April 6, 2006	**Group Art Unit:**	1627
Confirmation No.:	3491	**Examiner:**	Carter, Kendra D.
Title:	Methods and Compositions for the Treatment of CNS-Related Conditions		

Commissioner for Patents
P.O. Box 1450
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DECLARATION OF SID GILMAN, M.D., F.R.C.P., UNDER 37 C.F.R. §1.132

I, Sid Gilman, declare and state as follows.

1. I am the William J. Herdman Distinguished University Professor of Neurology at the University of Michigan, and Director of the Michigan Alzheimer's Disease Research Center. I am an attending neurologist in the University of Michigan Hospitals. I am certified by the American Board of Psychiatry and Neurology. I have authored approximately 500 scientific papers, book chapters and abstracts in the fields of neurology and neuroscience. My curriculum vitae is attached.

2. I am a paid consultant as a member of the Clinical Advisory Board of Adamas Pharmaceuticals, Inc., the assignee of this patent application, but I have not received stock options in the company.

3. I have been asked by Adamas Pharmaceuticals to read and review Ditzler, *Arnzneim.-Forsch./Drug Res.*, 1991, no. 8, pp. 773-780 and provide my opinion on how a person of ordinary skill in the art at the time of the invention claimed in U.S. Patent Application Serial No. 11/399,879 would understand the meaning of the Ditzler article, in particular the following disclosure:

> Adverse drug effects recorded by DOTES for memantine were agitation/excitation, increased motor activity, sleeplessness which, however, receded in the course of treatment. *These adverse effects represent an excessive*

pharmacodynamic effect resulting from a too rapid dose increase. (Abstract, emphasis added)

However, the adverse reactions recorded in DOTES/TWIS were not serious and were transient, and very probably the result of a too rapid dose increase at the beginning of treatment. *The dose should therefore be increased distinctly more slowly and adjusted to the individual situation* until the optimal effect has been reached. (p. 778, emphasis added)

To avoid adverse reactions such as restlessness, excitation and insomnia, the dose must be increased at a rate adjusted to the individual patient. (p. 780)

4. I have read and understood the cited portion and entire Ditzler article, the subject patent application, the pending claims, as well as the office action dated Feb. 8, 2011 and other cited references: Moebius (US 2004/0087658 A1) and Nurnberg et al., (US 5,382,601).

5. To arrive at my opinion, I rely on the plain language and disclosure of Ditzler, the general knowledge in the art and my own experience. I am and have been familiar since the 1990s with the therapeutic use of memantine, a NMDA receptor antagonist, and of donepezil, an acetyl cholinesterase inhibitor. I have prescribed each of these drugs, alone and in combination, to my patients to treat the symptoms of Alzheimer's Disease. I have served as a member of the Peripheral and Central Nervous System Drugs Advisory Committee (from 1983 until 2000), and I chaired the Committee from 1996 until 2000. I have been retained as a special consultant to the FDA in 5 year terms beginning in 2000. My current term runs from 2010 until 2015.

6. Ditzler describes side effects associated with the administration of memantine to Alzheimer's Disease patients in a study wherein memantine dose was increased over an eight day period (about 1 week), from a starting dose of 10 mg/day to a final dose of 30 mg/day. Ditzler reports that these side effects *"represent an excessive pharmacodynamic effect resulting from a too rapid dose increase"* and "*the dose should therefore be increased distinctly more slowly.*" He further adds that "this *dose must be increased at a rate adjusted to the individual patient.*"

7. The Examiner states that based on the above observations of Ditzler in light of Moebius "*one would have been motivated to provide memantine in an extended release form to avoid adverse effects"* (for example, page 8-9 of Office Action). She bases this upon

Ditzler's statement that, for memantine, "*the dose should therefore be increased distinctly more slowly*", and, I presume, Moebius' statement that memantine can be "*suitably formulated to give a controlled or postponed release.*" (¶ [0194].) The Examiner believes that these statements logically lead to the development of an extended release drug fitting the limitations of the claims of the Went et al. application. This belief, however, does not follow logically from the facts. The Examiners conclusion is inconsistent with what one of skill in the art would have understood from the Ditzler article in light of Moebius and from the known pharmacokinetic properties of memantine.

8. A person of ordinary skill in the art at the time the invention was made would have understood that Ditzler taught only that the period of 1 week between initiating therapy and arriving at the final dose was too short in his study, and that Ditzler's only guidance was "*to increase the dose distinctly more slowly*" beyond 1 week.

9. Ditzler's reference to a "*too rapid dose increase*" and "*to increase the dose distinctly more slowly*" does not refer to or suggest the use of any type of extended release formulation such as those described by Went et al., nor does he even reference the pharmacokinetics of memantine. Rather, Ditzler was referring to the 1 week time period between initiating therapy and arriving at the final dose. Thus, Ditzler may have suggested to one of skill in the art that the tolerability of immediate release memantine could be improved by implementing a more gradual schedule for increasing the dose of memantine, that is, by having a dose increase period longer than the 1 week used in the Ditzler study. Even on this point, Ditzler does not suggest how long the period in weeks needs to be, other than to say that it should be tailored to each individual patient. A plain reading of Ditzler supports my opinion. Moreover, a more gradual schedule for increasing memantine dose – over a period of 3 weeks versus the 1 week period used by Ditzler – became standard medical practice. Hence, the approved labeled dosing for FDA-approved immediate release memantine (Namenda) in the U.S. is 5 mg for the first week, 5 mg twice daily for the second week, 10 mg morning and 5 mg evening for the third week, and 10 mg twice daily thereafter.

10. Ditzler does not disclose nor suggest to one of skill in the art the method of the present invention. This invention provides an extended release memantine formulation with a

change in plasma concentration of memantine as a function of time (dC/dT) that is less than about 50% of the dC/dT of the same quantity of an immediate release form of memantine between the time period of 0 to Tmax of the immediate release form. Ditzler's reference to a "*too rapid dose increase*" would not suggest or motivate the use of any type of extended release formulation. Ditzler makes no reference to the pharmacokinetics of memantine nor does he in any manner suggest that there might be any connection between the *adverse drug effects* ([that] *represent an excessive pharmacodynamic effect*) and the *pharmacokinetics* of memantine (i.e. the plasma concentration versus time).

11. It does not follow logically that slowing the dose increase of memantine by weeks, (i.e., increasing the period between the initiation and final dose administered as proposed by Ditzler) would ever lead one to the use of extended release formulations of memantine (as described by Went et al.).

12. In sharp difference to the teachings of Ditzler, Went et al. made the surprising observation that the side effects of memantine were related to the initial rate of rise in memantine plasma concentration over the first several **hours** after dosing. Went et al. discovered that by modifying the release of memantine in a manner that slowed the initial rate of rise in plasma concentration over about 4-7 hours to a level that is less than about 50% of that of immediate release IR memantine, the side effects of memantine could be reduced. In addition to providing benefit over a range of doses such as 5-40 mgs/day, Went further teaches that this can lead to a once-daily administration of memantine at doses above 20 mg using the specified ER formulations developed by Went et al. The claimed benefits of Went et al. are contrary to the teachings of Ditzler, whose suggestion of *a dose that should be increased distinctly more slowly* led to the labeled dose titration over 3 weeks and a final daily dosing of memantine of 20 mg, given as 10 mg twice daily. Thus, Went et al.'s findings are entirely unanticipated from clinical practice at the time or indeed any prior art that I am aware of.

13. Thus, based on the plain meaning of Ditzler and my own clinical experience, it is my opinion that a person of ordinary skill in the art at the time the Went application was filed would have properly understood Ditzler as recommending an increase in the period

between initiation to final dose from ~ 1 week to the order of 3 weeks to alleviate the side effects. Given what was known about the pharmacokinetic and pharmacodynamic characteristics of memantine at the time of the invention, one would not have expected that extending the release of memantine, and in particular, slowing the rate of rise in memantine plasma concentration in the first few **hours** after administration would have any impact at all on tolerability. This could not have been inferred from Ditzler alone or in combination with Nurnberg and Moebius.

14. With respect to Nurnberg, who teaches a two-phase formulation of memantine, this reference does not contribute alone or in combination with Moebius and Ditzler to suggest or lead to the novel teaching of Went et al. The Nurnberg reference does not contain or suggest any ER formulation approximating the Went formulation, nor does he refer to any relationship between the pharmacokinetics of memantine and its side effects.

Summary

15. This invention provides a method of alleviating the well known side effects of memantine in an unanticipated way. Went et al. demonstrated that memantine formulations with a dC/dT of less than about 50% of IR memantine are well tolerated. They have thereby enabled a formulation of memantine that can be taken once daily without the previously problematic side effects. There is nothing in Ditzler, Moebius or Nurnberg, singly or in combination, that would motivate or teach the above.

16. 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.

Date: April 4, 2011

Sid Gilman

Sid Gilman, M.D., F.R.C.P.