IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	11/285,905	**Customer No.:**	72664
Applicant:	Gregory T. Went et al.	**Docket No.:**	522 US
Filed:	November 22, 2005	**Group Art Unit:**	4161
Confirmation No.:	9709	**Examiner:**	Carter, Kendra D.
Title:	Method and Composition for Administering an NMDA Receptor Antagonist to a Subject		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GAYATRI SATHYAN, Ph.D. UNDER 37 C.F.R. §1.132

I, Gayatri Sathyan, declare and state as follows:

1. I am a Senior Director of Clinical Pharmacology at Adamas India Pharmaceuticals, Pvt. Ltd, a wholly-owned subsidiary of Adamas Pharmaceuticals, assignee of the subject patent application. As part of my employment compensation, I have received stock options in Adamas Pharmaceuticals.

2. I have a Ph.D. from the University of Cincinnati's College of Pharmacy, Division of Pharmaceutics and Drug Delivery Systems. I have over 15 years of pharmaceutical industry experience. Prior to my employment with Adamas India I was employed for over 10 years by ALZA Corporation, a recognized leader in controlled-release drug delivery systems. While at ALZA, I was involved in the development of oral controlled-release products and was lead clinical pharmacologist responsible for NDAs and EX-US/Worldwide submissions for 5 products. I am an author of over 30 publications in the fields of pharmacology and pharmacokinetics. My publication list is attached as Appendix A.

3. I have read the subject patent application, the pending claims, the Patent Office Action dated 03/23/2009 and the cited references (i.e. US Patent No. 6,194,000 to Smith et al., and Timmermans et al., Drug Dev Ind Pharm. (1998) 6:517-25). For reasons explained below, it is my opinion that the cited references do not suggest or make obvious to a person of ordinary skill in the art a method of avoiding side-effects in a patient initiating memantine therapy by administering to the patient a therapeutically effective dose of memantine from initiation of therapy without dose escalation, or reaching a therapeutically effective steady state plasma concentration of memantine within fifteen days from initiating therapy. It is my expert opinion

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that the person of ordinary skill in the field would not have found it obvious and be motivated to use extended release as a substitute for dose escalation in view of the following facts.

4. A person having ordinary skill in the field of developing improved formulations and dosing regimens for existing drugs will be familiar with the clinical studies published for the drug they are developing. The skilled person will know the drug's pharmacokinetic properties (e.g. rate of absorption, time to maximum plasma concentration, elimination half-life, etc.), prior dosage forms and methods of administration, indications, and side-effect profiles. With respect to memantine, the skilled person in 2005 would have known from the relevant literature that memantine is escalated at initiation of therapy to avoid psychotomimetic side-effects:

> In contrast with some other NMDA-receptor antagonists (e.g. PCP, MK-801), memantine is associated with minimal psychotomimetic side-effects (e.g. delusions, hallucinations and depersonalization), ataxia and motor incoordination, ***providing that the dose is properly titrated over a period of 3-4 weeks***. (Eleanor Bull, *Drug review – Memantine,* Drugs in Context (2005) I(I):1-40; emphasis added; article attached as Appendix B).

5. The Office Action dated Mar. 23, 2009, in the paragraph bridging pages 4-5, alleges:

> To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Smith et al. and a method to avoid side-effects because Smith et al. teaches a sustained release form of memantine and Timmermans et al. teach that sustained release dosage forms are effective in reducing the incidence of concentration-related side effects, e.g., emesis, and of behavioral symptoms, restlessness, discomfort and indisposition (see abstract, lines 6-9).

For reasons given below, in my opinion, this is an incorrect assessment of the state of the art in 2005. In fact, the person of ordinary skill would not have found Timmermans et al. useful with respect to how to improve the dosing schedule of memantine.

6. It is well-known in the field of pharmacokinetics that sustaining release of a drug with a short time to maximum plasma concentration (Tmax) and a short elimination half-life will prolong the duration of action of the drug, allowing for less frequent dosing. It is also known that sustaining release of such a drug may also reduce drug concentration-related side effects because, typically, the sustained release (SR) formulation achieves a maximum plasma concentration (Cmax) that is lower than that of the immediate release (IR) formulation of the drug at the same dose level. This is illustrated in Fig. 1 of the article by Lloyd N. Sansom entitled "Oral extended-release products", attached as Appendix C, in which the curve with the three peaks depicts a theoretical drug concentration profile of an IR form of a drug administered three times daily and the dotted line curve depicts an SR form of the same drug administered once daily at the same daily dose as the IR form. The IR form's Cmax materially exceeds the necessary therapeutic concentration, and may result in plasma concentrations at which side effects occur, whereas the SR form has a substantially reduced Cmax while maintaining drug concentration at therapeutic levels.

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7. Timmermans et al demonstrated that short Tmax and half-life are the case with ucb 11056 (see Abstract: *All SR [sustained release] dosage forms were seen to be effective in prolonging the relatively short biological half-life of the compound and in reducing the incidence of concentration-related side-effects…*). Timmermans et al. do not disclose the precise half-life of an IR formulation of ucb 11056, but from the graph on p. 520, the terminal half-life appears to be in the range of about 1.5-2.5 hours. Table 1 shows that the Tmax of an immediate release (IR) formulation of the drug is 1.1 ± 0.5 hrs. Assuming once or twice per day dosing, all or most of ucb 11056 would be metabolized or eliminated prior to a subsequent dose given this short half-life. This is in contrast to memantine which accumulates to a level significantly higher than the concentrations observed after a single dose, due to a much longer half-life.[1] Table 1 in Timmermans also shows the reductions in maximum concentration (Cmax) of the drug that were achieved by sustaining release of ucb 11056. In each case, the Cmax of the SR formulation was less than half that of the IR formulation at the same dose. Timmermans clearly appreciated the relationship between Cmax and the side effects (emesis) as noted at the top of page 523 in the second column: "The IR capsule study group showing the highest ucb 11056 peak plasma concentration is most frequently affected by emesis… whereas no emesis is observed following the SR pellets batch 11 dosing that produces a comparatively 10-times lower Cmax value." Indeed, the authors state on p. 523 column 2, paragraph 4, that "Emesis can thus be defined as a dose-dependent effect or perhaps more rigorously speaking in the case of SR forms, as a concentration-dependent effect."

8. There is nothing in Timmermans that would lead one skilled in the art to consider this reference when making improvements to a memantine formulation because it is well-known in the art that memantine's side effects occur upon initiation of therapy with the IR formulation when plasma concentrations of the drug are well below therapeutically-effective levels. Further, the pharmacokinetic properties of memantine are very different from that of Timmermans' drug. Referring to the Table 1 on p. 20 of the article attached as Appendix B, in contrast to the very short 1.1 hour Tmax of Timmermans' drug, memantine has a Tmax of 3-8 hours; and, in contrast to the 1.5-2.5 hour half-life of Timmermans drug, memantine has a half-life of about 60-100 hours. Because of memantine's relatively long Tmax and elimination half-life, the Cmax of a single dose of an SR formulation of memantine will be very close to the Cmax of a single dose of an IR formulation of the same strength at equivalent exposure. This is because very little drug is eliminated from a patient before the Cmax of an SR formulation is reached. Thus the substantial reduction in Cmax that was achieved by sustaining release of Timmermans' drug will not happen when release of memantine is sustained. This point is illustrated in the attached Appendix D, which is an annotated version of FIGS 1A and 1B from the application. Referring to FIG 1A, pharmacokinetic modeling (Software:GastroPlus™) shows that administering a

[1] This is illustrated in the attached Appendix D, which is an annotated version of FIGS 1A and 1B from the application. Referring to Fig. 1B, pharmacokinetic modeling software (GastroPlus™) shows that at 24 hours after administration of a 22.5 mg dose of an SR memantine formulation (5001-6701), a patient will have a memantine plasma concentration of just above 0.02 μg/ml. After administration of the 2nd dose, the patient will achieve a memantine plasma concentration of about 0.04 μg/ml, and so on, until a steady state plasma concentration is reached.

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22.5mg dose of an SR memantine formulation (5001-6701) to a patient initiating memantine therapy will achieve a maximum plasma concentration that is approximately 95% that of a 20 mg dose of an IR memantine formulation (Namenda). Thus, one of ordinary skill in the art would not consider Timmermans et al. relevant to memantine as 1) there is no apparent need to prolong the duration of action of memantine, 2) one would not expect an SR formulation of memantine to substantially reduce Cmax, and consequently concentration-related side effects, and 3) unlike Timmermans' drug, the Cmax of memantine increases with each day of dosing until a steady-state plasma concentration is reached.

9. To the extent one of ordinary skill in the art would have considered the Timmermans et al. relevant to memantine therapy, the reference would have taught away from administering a therapeutically effective dose of Smith's SR memantine formulation to a patient initiating memantine therapy because: 1) it was known in the art, as evidenced by the Appendix B review article, that memantine should be titrated over 3 to 4 weeks to avoid side-effects; and 2) Timmermans teaches to reduce maximum plasma concentration in order to reduce side-effects. One of ordinary skill in the art would have been able to determine that by eliminating the dose escalation of memantine, even if formulated for sustained release, initial maximum plasma concentrations would significantly increase compared to the Cmax values initially achieved by following the medically-accepted practice of initiating memantine therapy at a sub-therapeutic dose of 5mg. The principle applied by Timmermans, that side effects of a drug can be eliminated in some cases using sustained release formulations, when applied to memantine actually suggests to the person of ordinary skill to avoid substituting a "full-strength" ER formulation for the state of the art IR dose escalation. The initiation of therapy with the ER memantine of the subject patent application results in a significantly higher Cmax than the standard dose escalation. This point is also illustrated in FIG 1A of Appendix D, which, compared to the figure in the application, adds a 3rd curve simulating a single-dose plasma concentration curve for 5 mg Namenda. The graph illustrates that by administering a therapeutic dose (e.g. 22.5mg) of an SR memantine formulation (5001-6701) to a patient initiating memantine therapy, a maximum plasma concentration will be achieved that is approximately four times greater than that achieved by a 5 mg dose of IR memantine. This point is further illustrated by the attached Appendix E, which shows the modeled profile (Software: GastroPlus™) of a 22.5 mg strength of an SR memantine formulation, ADS-5002, administered without dose escalation once daily for four days compared to once daily dosing with 5mg Namenda in accordance with the recommended initial dosing schedule. On day four, the Cmax achieved by ADS-5002 is approximately 0.060 μg/ml, whereas the Cmax achieved by 5mg NAMENDA is about 0.018 μg/ml. Thus, the person of ordinary skill trying to apply Timmermans to memantine side effect control would not start the therapy at the much higher memantine concentrations even if they were in ER form.

10. The Office Action dated Mar. 23, 2009, made the remark on p. 5, line 11, that "because the overlap in administration the dosage is naturally escalated." While daily administration of a sustained release oral dosage form comprising memantine will naturally result in increasing plasma concentration of memantine each day (due to its long half-life) until a steady-state plasma concentration is reached, one skilled in the art would not consider this to be "dose escalation".

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Dose escalation is when the daily dose administered to a patient is higher than a previously administered daily dose. Fig 1B in the attached Appendix D compares the pharmacokinetic profile of memantine when administered in accordance with standard dose-escalation with the profile of a sustained release oral dosage form administered at a therapeutically effective daily dose from initiation of therapy (Namenda Ramp profile vs. 5001-6701 profile, respectively), and shows that the two dosing regimens yield very different results. With the 5001-6701 dosing regimen, a therapeutically effective steady state plasma concentration is reached about 15 days after initiating therapy. In comparison, using the standard dose-escalation regimen provided in the approved Namenda product label, a therapeutically effective steady state plasma concentration is reached about 37 days after initiating therapy. This illustrates that a non dose-escalating regimen using a sustained release dosage form is not pharmacokinetically or therapeutically equivalent to a dose-escalation regimen, and one of ordinary skill in the art would not consider the two regimens to be generally substitutable for each other.

11. The Office Action dated Mar. 23, 2009, further remarked on p. 6, line 17, that "regardless if the patient is administered the drug in dose escalation or all at once in a sustained release form, it is obvious that both will reduce side effects compared to offering the drug at the therapeutic amount in a non-sustained release form." However, this statement is inaccurate. If a drug's side-effect is purely concentration-dependent then sustaining release of the drug will not necessarily reduce the side effects, but may just delay the occurrence of the side effects until the concentration at which the side effects occur is reached. This is evident from Timmermans et al:

> The IR capsule-dosed animals are seen to vomit soon after drug administration (44+/- 15 min).... For the SR matrix and SR pellets batch 15, the animals having vomited are among the more exposed ones, which conforms to expectation because this side effect is known to be concentration dependent.... In addition, the shorter the Tmax value, the sooner the onset time of vomiting. ***The SR dosage forms therefore exhibit a delayed pattern of side effects in comparison with the IR formulation***. (Timmermans et al., p. 523, col 1, line 3 to col 2, line 16; emphasis added).

Thus, Timmermans' SR formulation does not appear to reduce the side effects at a given concentration. In other words, the Timmermans SR formulation did not reduce side effects by slowing uptake of the drug – the same side effects that were seen with the IR formulation of the drug were also seen with some of the SR formulations, albeit delayed, provided a high enough concentration of the drug was achieved.

12. Further, it is well-known in the art that SR formulations are often dose-escalated. RAZADYNE, COREG CR, and WELLBUTRIN SR, are all examples of SR formulations that require dose escalation at initiation of therapy to avoid side effects[2]. Another example is REQUIP XL. Obviously, sustained release technology does not necessarily eliminate the need to dose escalate drugs to avoid side effects.

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[2] The response filed Dec. 23, 2008, also listed DITROPAN XL® as a drug that is titrated at initiation of therapy. However, with some patients the 5mg starting dose may be therapeutically effective such that they are not subsequently titrated to higher levels of the drug.

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