IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JANSSEN PHARMACEUTICA N.V., JANSSEN, L.P., and SYNAPTECH, INC.,	)	
Plaintiffs,	)	
v.	)	Civ. Action No._____
PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC.	)	
Defendants.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P. (collectively, "Janssen"), and Synaptech, Inc. (collectively, "Plaintiffs"), by their attorneys, for their complaint against Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. (collectively, "Par"), allege as follows:

The Parties

1. Plaintiff Janssen Pharmaceutica N.V., a wholly owned subsidiary of Johnson & Johnson, is a corporation organized and existing under the laws of Belgium and has its principal place of business at Turnhoutseweg 30, B-2340 Beerse, Belgium.

2. Plaintiff Janssen, L.P., a wholly owned subsidiary of Johnson & Johnson, is a limited partnership organized and existing under the laws of the State of New Jersey and has its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560.

3. Plaintiff Synaptech, Inc. ("Synaptech") is a company organized and existing under the laws of the State of New York and has its principal place of business care of Schwartz & Salomon, P.C., 225 Broadway, New York, New York 10007.

4. Upon information and belief, Defendant Par Pharmaceutical, Inc. is a corporation organized and existing under the laws of the State of Delaware and has its principal place of business at One Ram Ridge Road, Spring Valley, New York 10977. Par Pharmaceutical, Inc. is registered to do business and does business in the State of Delaware.

5. Upon information and belief, Defendant Par Pharmaceutical Companies, Inc. is a corporation organized and existing under the laws of the State of Delaware and has its principal place of business at One Ram Ridge Road, Spring Valley, New York 10977. Par Pharmaceutical Companies, Inc. is registered to do business and does business in the State of Delaware. Par Pharmaceutical Companies, Inc. is the ultimate parent of Par Pharmaceutical, Inc., and Par Pharmaceutical, Inc. is a wholly owned subsidiary of Par Pharmaceutical Companies, Inc.

6. Upon information and belief, Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. collaborated in the research and development of Par's Abbreviated New Drug Application ("ANDA") No. 77-604 for galantamine hydrobromide tablets, continue to collaborate in seeking approval of that application from the Food and Drug Administration ("FDA"), and intend to collaborate in the commercial manufacture, marketing, and sale of galantamine hydrobromide products, including commercial marketing and sale in the State of Delaware, in the event that FDA approves

Par's ANDA No. 77-604. Upon information and belief, Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. collaborate in the manufacture, marketing, and sale of many pharmaceutical products, including numerous generic prescription drug products manufactured and sold pursuant to an approved abbreviated new drug application, that are marketed and sold to customers in the State of Delaware.

Jurisdiction and Venue

7. This is a civil action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code, for infringement of United States Patent No. 4,663,318 ("the '318 patent"). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

8. Par Pharmaceutical, Inc. is subject to personal jurisdiction in this judicial district by virtue of, *inter alia*, its having incorporated in Delaware, having conducted business in the State, having availed itself of the rights and benefits of Delaware law, and having engaged in substantial and continuing contacts with the State.

9. Par Pharmaceutical Companies, Inc. is subject to personal jurisdiction in this judicial district by virtue of, *inter alia*, its having incorporated in Delaware, having conducted business in the State, having availed itself of the rights and benefits of Delaware law, and having engaged in substantial and continuing contacts with the State.

10. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

Regulatory Requirements for Approval of New and Generic Drugs

11. Any person wishing to market a pioneering drug – that is, a new drug that has not previously been approved by FDA – must first file a New Drug Application ("NDA") with FDA demonstrating that the drug is safe and effective for its intended use. 21 U.S.C. § 355(b). To secure approval of an NDA, the NDA applicant must, among other things, collect and submit to FDA extensive animal and human clinical trial data at a substantial cost of time and money.

12. A person wishing to market a generic copy of a pioneering drug that previously has been approved by FDA may follow a truncated approval process by filing an abbreviated new drug application for a generic version of the drug. In the ANDA, the applicant must demonstrate, among other things, bioequivalence of the generic copy of the pioneering drug. 21 U.S.C. § 355(j)(2)(A)(iv). To demonstrate bioequivalence, the ANDA applicant must show that the rate and extent of absorption of the therapeutic ingredient in the generic drug does not significantly differ from that in the pioneering drug, or, if the rate of absorption differs, that such difference is intentional, is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. 21 U.S.C. § 355(j)(8)(B).

13. However, unlike an NDA applicant, an ANDA applicant is not required to include safety and effectiveness data. The ANDA applicant is not required, for example, to conduct well-controlled clinical trials concerning the safety and effectiveness of the proposed drug. Instead, the ANDA applicant is permitted to piggy-

back on the safety and effectiveness data developed and submitted by the approved NDA holder. 21 U.S.C. § 355(j).

14. Nor does an ANDA applicant establish any new conditions of use for the proposed drug product. Instead, an ANDA applicant may seek approval only for conditions of use that previously have been approved in connection with an approved NDA. 21 U.S.C. § 355(j)(2)(A)(i).

15. No person may market in the United States a new drug without an approved NDA or a generic version of a drug without an approved ANDA. 21 U.S.C. § 355(a).

Plaintiffs' Approved Drug Product

16. Janssen is the holder of an approved new drug application, NDA No. 21-169, for galantamine hydrobromide tablets. That NDA was approved by FDA on February 28, 2001 and covers three strengths of tablet – Eq. 4 mg base, 8 mg base, and 12 mg base. The sole indication or condition of use for which galantamine hydrobromide tablets are approved in NDA No. 21-169 is the treatment of mild to moderate dementia of the Alzheimer's type.

17. Pursuant to FDA's approval, Janssen currently markets galantamine hydrobromide tablets for the treatment of mild to moderate dementia of the Alzheimer's type under the trademark RAZADYNE®. Until this year, Janssen marketed its galantamine hydrobromide tablets under the trademark REMINYL®.

18. FDA has listed the '318 patent in the Orange Book – formally known as Approved Drug Products With Therapeutic Equivalence Evaluations – in connection with NDA No. 21-169.

19. The '318 patent qualifies for listing in the Orange Book in connection with NDA No. 21-169 because it claims an approved use of the drug product that is the subject of that NDA. Par has never challenged the listing of the '318 patent in the Orange Book.

Par's ANDA

20. Par has represented that on or before May 17, 2005, it submitted to FDA an ANDA (ANDA No. 77-604) and paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(2)(A)(vii)(IV), for galantamine hydrobromide tablets purportedly bioequivalent to Plaintiffs' RAZADYNE® products. The purpose of Par's ANDA and paragraph IV certifications is to obtain approval under section 505(j) of the FDCA to engage in the commercial manufacture and sale of its proposed galantamine hydrobromide tablets before the expiration of the patents listed in the Orange Book for Janssen's NDA No. 21-169. Hence, Par's purpose in submitting ANDA No. 77-604 is to market in the United States the galantamine hydrobromide products described therein before expiration of the '318 patent.

21. Upon information and belief, the sole condition of use for which Par seeks approval in its ANDA No. 77-604 for its proposed galantamine hydrobromide tablets is the treatment of mild to moderate dementia of the Alzheimer's type, the same condition of use as that approved in Janssen's NDA No. 21-169.

22. Upon information and belief, the sole indication set forth in the proposed labeling submitted by Par in its ANDA No. 77-604 for its proposed galantamine hydrobromide tablets is the treatment of mild to moderate dementia of the Alzheimer's type, the same indication as that set forth in the approved labeling for Plaintiffs' REMINYL® and RAZADYNE® tablets.

Count 1: Patent Infringement

23. Plaintiffs reallege paragraphs 1 through 22 above as if fully set forth herein.

24. On May 5, 1987, the United States Patent and Trademark Office duly and legally issued the '318 patent, entitled "Method of Treating Alzheimer's Disease." The term of the '318 patent runs through December 14, 2008. A true and correct copy of the '318 patent is attached hereto as Exhibit A.

25. Synaptech is the owner of the '318 patent.

26. Janssen is the exclusive licensee under the '318 patent, pursuant to an exclusive license agreement between Synaptech and Janssen, of the right to develop, make, have made, keep, use, market, sell, and/or dispose of certain pharmaceutical preparations containing galantamine hydrobromide to treat Alzheimer's disease in the United States and other territories. Pursuant to that exclusive license, Janssen currently markets galantamine hydrobromide tablets in the United States under the trademark RAZADYNE® and previously marketed galantamine hydrobromide tablets in the United States under the trademark REMINYL®. The conditions of use for which RAZADYNE® and REMINYL® are approved fall within one or more of the claims of the '318 patent.

27. As exclusive licensee, Janssen is authorized to enforce the '318 patent.

28. The conditions of use for which Par seeks approval in its ANDA No. 77-604 fall within one or more of the claims of the '318 patent. If approved, use of Par's proposed galantamine hydrobromide products in accordance with the proposed labeling for those products submitted in ANDA No. 77-604 would constitute a use of the product claimed in one or more of the claims of the '318 patent.

29. Par Pharmaceutical, Inc. is liable for infringement of the '318 patent under 35 U.S.C. § 271(e)(2)(A) by virtue of its filing ANDA No. 77-604 with a paragraph IV certification seeking FDA approval of ANDA No. 77-604 prior to expiration of the '318 patent. Par Pharmaceutical Companies, Inc. is liable for infringement of the '318 patent under 35 U.S.C. § 271(e)(2)(A) by virtue of its causing ANDA No. 77-604 with a paragraph IV certification to be filed with FDA seeking approval of ANDA No. 77-604 prior to expiration of the '318 patent.

30. Upon information and belief, if approved, Par's galantamine hydrobromide products for which approval is sought in Par's ANDA No. 77-604 will be administered to human patients in a therapeutically effective amount for treatment of mild to moderate dementia of the Alzheimer's type, which administration would constitute direct infringement of the '318 patent. Upon information and belief, this infringement will occur at Par's behest, with its intent, knowledge, and encouragement, and Par will actively induce, encourage, aid, and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '318 patent.

31. Par's offer for sale or sale in the United States, or importation into the United States, prior to expiration of the '318 patent, of the galantamine hydrobromide products for which approval is sought in ANDA No. 77-604, would actively induce and contribute to infringement of the '318 patent, and Par would be liable as an infringer under 35 U.S.C. §§ 271(b) and/or (c). Par's use in the United States of the galantamine hydrobromide products in accordance with the labeling for which approval is sought in ANDA No. 77-604 prior to expiration of the '318 patent would infringe the '318 patent, and Par would be liable as an infringer under 35 U.S.C. § 271(a).

32. Par had actual and constructive notice of the '318 patent prior to filing its ANDA No. 77-604, and Par's infringement of the '318 patent has been, and continues to be, willful.

33. Plaintiffs will be irreparably harmed if Par is not enjoined from infringing or actively inducing or contributing to infringement of the '318 patent. Plaintiffs do not have an adequate remedy at law.

Prayer For Relief

WHEREFORE, Plaintiffs seek the following relief:

A. A judgment that Par has infringed the '318 patent under 35 U.S.C. § 271(e)(2)(A);

B. A judgment providing that the effective date of any FDA approval of the Par ANDA No. 77-604 for galantamine hydrobromide Eq. 4 mg base, 8 mg base, and 12 mg base tablets be not earlier than the expiration date of the '318 patent;

C. A judgment declaring that Par's manufacture, use, sale, offer for sale, or importation into the United States of the galantamine hydrobromide products for which approval is sought in ANDA No. 77-604 would constitute infringement of the '318 patent, or would induce or contribute to such infringement, pursuant to 35 U.S.C. § 271 (a), (b), and/or (c);

D. A permanent injunction enjoining Par and its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from making, using, selling, or offering to sell in the United States, or importing into the United States, the galantamine hydrobromide tablets for which approval is sought in ANDA No. 77-604, or any galantamine hydrobromide product that infringes or induces or contributes to the infringement of the '318 patent, until expiration of that patent;

E. A finding that this is an exceptional case, and an award of attorneys' fees in this action pursuant to 35 U.S.C. § 285;

F. An award of costs and expenses in this action; and

G. Such further and other relief as this Court determines to be just and proper.

ASHBY & GEDDES

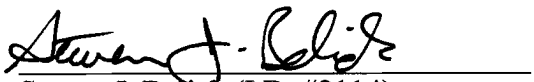

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EXHIBIT A

United States Patent [19]

Davis

[11] **Patent Number: 4,663,318**

[45] **Date of Patent: May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] Inventor: **Bonnie Davis**, 17 Seacrest Dr., Huntington, N.Y. 11743

[21] Appl. No.: **819,141**

[22] Filed: **Jan. 15, 1986**

[51] **Int. Cl.**[4] **A61K 31/55**

[52] **U.S. Cl.** **514/215**

[58] **Field of Search** 514/215

[56] **References Cited**

PUBLICATIONS

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Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Ladas & Parry

[57] **ABSTRACT**

Alzheimer's disease may be treated with galanthamine.

7 Claims, No Drawings

METHOD OF TREATING ALZHEIMER'S DISEASE

GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163–8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anesth. Scand. 24:166–168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physcial form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water

at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1–50 mg/ml more commonly 5–40 mg/ml, for example, 5–30 mg/ml or 10–40 mg/ml, typically 20–30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5–1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5–5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50–300 mg per day to a patient of a body weight of 40–100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100–600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacyin Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945–952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to

administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5–1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50–300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10–2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100–600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

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