Attorney Docket No. 9050- 56

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Moore

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Thomas NAJARIAN
Serial No.: 09/593,555 Group Art Unit: 1623
Filing Date: June 14, 2000 Examiner: Leigh MAIER
Title: COMBINATION THERAPY FOR EFFECTING WEIGHT LOSS AND TREATING OBESITY

DECLARATION OF THOMAS NAJARIAN SUBMITTED PURSUANT TO 37 CFR § 1.132

Commissioner for Patents
Washington, DC 20231

Sir:

I, Thomas Najarian, hereby declare that:

1. I am an inventor of the subject matter claimed in the above-referenced U.S. patent application.

2. Reference may be had to my *curriculum vitae*, attached hereto as Appendix A, for detailed information concerning my education and work experience. Briefly, I received Bachelor of Science and Master of Science degrees in mechanical engineering in 1970 from the Massachusetts Institute of Technology, and an M.D. in 1974 from Harvard Medical School. After I obtained my doctorate, I spent three years in residency at the Jamaica Plain VA Medical Center, specializing in internal medicine. I have 25 years of experience in the treatment of obesity, including two years as a consultant to Interneuron Pharmaceuticals and two years as Medical Director at Interneuron Pharmaceuticals, the developers of Redux, the weight loss medication.

3. I have been interested in the treatment of obesity for 25 years and am considered one of the leading experts in obesity treatment in the United States. As Medical Director at Interneuron Pharmaceuticals, I designed and conducted one of the critical studies that analyzed the

relationship of the weight loss drug Redux to heart valve problems. Redux was eventually withdrawn from the market because of these heart valve problems. In addition, I have prescribed or evaluated practically all of the weight loss treatments that have been devised for the past 25 years.

4. I have been requested to review the above-referenced patent application and the pending claims, the Office Action mailed April 23, 2002, the Amendment Under 37 CFR § 1.112 which accompanies this declaration, and the references cited by the Examiner in the Office Action: the Physician's Desk Reference (49th edition, 1995); Shank, US Patent No. 6,071,537; Keown, et al., US Patent No. 5,543,405; Seed, US Patent No. 4,895,845; and Wierzbicki, et al., US Patent No. 5,266,591.

I have been also been asked to provide this declaration in order to assist the Examiner in understanding the fundamental distinctions between the subject matter claimed in the above-referenced application and that disclosed in five cited references, as well as explain the surprising observations I have made in patients who have been treated with the topiramate/phentermine combination.

5. It is my understanding that all claims currently pending were rejected as being unpatentable over various combinations of the five cited references, on the ground that the references render obvious the combination therapy of a sympathomimetic agent and an anticonvulsant sulfamate derivative for weight loss as claimed in the above-referenced patent application.

6. In connection with the present analysis, I have reviewed the above-referenced patent application and the pending claims, the April 23, 2002 Office Action, the accompanying Amendment Under 37 CFR § 1.112, and the cited Physician's Desk Reference, Shank, Keown, Seed, and Wierzbicki references. My opinion as set forth herein is based on my understanding of the claimed invention and the cited references, and is drawn from my knowledge of the treatment of obesity.

7. The question to which I have directed my attention is whether the claimed combination and its use to effect weight loss is "obvious" over the cited references. I have been informed that "obviousness" in this context is intended to mean that the differences between the subject matter sought to be patented and that taught or suggested in the references are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the pertinent art, as of the effective filing date of the patent application or earlier.

8. The pending claims are directed to a method for effecting weight loss in a subject by administering (for a period of about 12-18 months) a combination of therapeutically effective amounts of a sympathomimetic agent and an anticonvulsant sulfamate derivative (Claim 1). An exemplary sympathomimetic agent is phentermine (e.g., Claims 2-5) and an exemplary anticonvulsant sulfamate derivative is topiramate (e.g., Claims 6-7).

There are also claims directed to a method of treating a subject with Syndrome X (Claim 14) and a method of treating side effects of obesity (Claim 15) using this combination. There are claims to pharmaceutical compositions (Claims 16 and 77) and kits (Claims 17 and 98) containing this combination.

9. By contrast, the references disclose: the use of phentermine, alone, to treat obesity (Physician's Desk Reference); the use of topiramate, alone, to treat obesity (Shank); the use of sympathomimetic agents in combination with mineral cation salts or chelates of trivalent and hexavalent chromium or vanadium to facilitate weight loss (Keown); the use of a rauwolfia alkaloid/antidepressant/optional sympathomimetic anorexic agent or antidepressant/sympathomimetic anorexic agent combination for facilitating weight loss (Seed); and the use of ethanolamine benzoate compounds to treat Syndrome X (Wierzbicki).

It is my opinion that methods using and compositions containing a sympathomimetic agent/anticonvulsant sulfamate derivative combination for weight loss or Syndrome X are not obvious over the cited references, because there is nothing to suggest this particular combination of therapeutic agents. In fact, based upon the complications experienced with other combination therapies for weight loss (e.g., phen-fen), combination therapies as a whole, can not be said to be obvious over disclosures that describe either a monotherapy (Physician's Desk Reference and Shank) or a different combination (Keown and Seed) of weight loss drugs.

For these reasons, then, it is my opinion that the claimed invention is nonobvious over the Physician's Desk Reference, Shank, Keown, Seed, and Wierzbicki, in that the references, viewed individually or combined, fail to suggest the claimed combination therapy.

10. Furthermore, the above-referenced patent application is premised on the important and unexpected finding that the combination of an anticonvulsant sulfamate derivative with a sympathomimetic agent provides improved weight loss and with fewer side effects than experienced when each drug is administered alone.

A. The claimed combination has surprisingly fewer side effects than the individual drugs.

Topiramate is currently marketed by Johnson and Johnson Corporation ("J&J") under the tradename Topamax® as an anticonvulsant. J&J has tried to develop this drug as an obesity treatment, and recently completed several large studies (several hundred people in each trial) to evaluate topiramate as an obesity treatment. A few months ago after these studies were completed, J&J abandoned the effort because of the high drop-out rate in the topiramate arm of the study. Although patients receiving topiramate achieved a weight loss of about 12% at the one year mark (using doses of 400-800 mg per day), the drop-out rate due to topiramate's side effects was about 25%, which is much too high for a drug that will likely be used by millions of people in the US. Most of the side effects were dose related and included tingling of the hands and feet, sedation, difficulty concentrating, and memory problems. These are unacceptable in a population of people who are mostly working members of society.

I had also evaluated topiramate with my patients, using even lower doses than in the J&J studies. My patients experienced similar side effects, even with topiramate doses as low as 100-200 mg per day. These side effects made the drug unacceptable as a weight loss treatment. In these same patients, over and over, I surprisingly found that the addition of a sympathomimetic agent such as phentermine greatly diminished the side effects of the topiramate. Further, this allowed patients who, previously, could not tolerate topiramate, to be able to take topiramate in combination with phentermine. I have also had patients who previously had difficulty tolerating phentermine when administered alone as a weight loss treatment because it was too stimulating and caused insomnia, even when taken in the morning as a single dose. These same patients

could tolerate phentermine when combined with topiramate, since both drugs nicely cancel out each other's side effects.

The preliminary success of this combination prompted me to file the above-identified patent application. It was surprising that the combination of two agents, each of which had unpleasant side effects when administered alone, was better tolerated among weight loss patients because the individual side effects were canceled out by the combination. This was surprising since the "phen-fen disaster" (heart damage associated with the phentermine-fenfluramine combination therapy for weight loss) suggested to those of us in the obesity treatment field, that combination therapies for weight loss could have serious side effects.

B. The claimed combination provides greater weight loss than currently available products.

The combination of an anticonvulsant sulfamate derivative such as topiramate with a sympathomimetic agent such as phentermine, as in the presently claimed invention, has provided patients with a weight loss of about 20% after one year. Furthermore, lower doses of phentermine and topiramate are used than when the drugs are administered alone, thus providing for a synergistic effect. The following table provides weight loss data from patients treated with a topiramate (100-200 mg/day) and phentermine (7.5-15 mg/day) combination therapy of the invention.

Topiramate and Phentermine (Exemplary combination of the instant invention)

Treatment Group	baseline	up to 100 days	100-200 days	201-365 days
N	46	51	33	18
Baseline BMI	--	37.3	38.6	37.6
Weight loss lbs up to 100 days	--	15.0	19.2	19.6
Weight loss lbs at 100-200 days	--	--	26.4	28.1
Weight loss lbs at 201-365 days	--	--	--	39.3
Mean % weight	--	7%	11%	17%
% patients losing ≥5%	--	67%	94%	100%
% patients losing ≥10%	--	14%	58%	78%

The current treatments for obesity are Xenical® (orlistat, Roche Pharmaceuticals) with a weight loss of 2% greater than placebo at one year and Meridia® (sibutramine hydrochloride monohydrate, Abbott Laboratories) with a weight loss of 5% greater than placebo at one year.

The population and doctors in this country desperately need a better treatment. Many of my patients have been on these other treatments and there is no comparison with efficacy and with patient satisfaction. The patients are much happier with the present invention because of the greater weight loss and fewer side effects. I have now treated more than 200 patients with the topiramate/phentermine combination, some of whom have been on treatment for 3 years. Here are some comparison figures for the treatments with Xenical and Meridia.

Treatment Group	Xenical (Intent-to-treat)	Placebo (1 year data)
N	1561	1119
Weight loss lbs at month 6	12.4	6.2
Weight loss lbs at month 12	13.4	5.8
Mean % weight	--	---
% patients losing ≥5%	45%	---
% patients losing ≥10%	20%	---

Treatment Group	Meridia (Intent-to-treat)	Placebo (6 months to 1 year data)
N	302	299
Weight loss lbs at month 6	12.1	2.0
Weight loss lbs at month 12	14.0	3.5
Mean % weight	--	---
% patients losing ≥5%	~60	---
% patients losing ≥10%	--	---

The average weight loss at 100-200 days for treatment with the topiramate/phentermine combination of the invention was 26.4 lbs. On the other hand, these same figures for treatment with Xenical and Meridia at 6 months were only 12.4 lbs and 12.1 lbs, respectively. The average weight loss at 201-365 days for the combination treatment of the invention was 39.3 lbs. On the other hand, these same figures for treatment with Xenical and Meridia at 12 months, were only 13.4 lbs and 14 lbs, respectively.

The percentage of patients losing at least 10% of their starting weight at 12 months with the combination treatment of the invention was 78%. On the other hand, this same figure for treatment with Xenical was only 20%. The percentage of patients losing at least 5% of their

starting weight at 12 months with the combination treatment of the invention was 100%. On the other hand, this same figure for treatment with Meridia was only 60%.

C. The claimed combination provides fewer adverse side effects than currently available products.

While patients treated with Meridia can experience an increase in blood pressure of a few mm of Hg, the topiramate/phentermine combination of the invention markedly lowers blood pressure. Surprisingly, when patients take only one of the drugs such as topiramate because of allergic reaction or past intolerance to phentermine, their blood pressure is not affected as much even when they have good weight loss. For example, one of my patients had high blood pressure when being treated with topiramate, alone. When she took phentermine with topiramate, her blood pressure averaged 10 points lower systolic and 8 points lower diastolic.

When patients take the topiramate/phentermine combination of the invention, I have frequently been able to stop many of their blood pressure medications at the start of treatment even when their starting blood pressures are higher than 140/90 and despite the discontinuation of diuretics and blood pressure medications, they return on follow up visits with consistently lower blood pressures. This is an unexpected finding with this treatment. I have never seen any treatment work like this before.

As well as having experience with obese patients who wish to lose weight, I have significant experience with diabetic or cardiac patients who wish to lose weight for underlying health reasons. I had initial concerns with regard to administering phentermine to patients who had angina or prior myocardial infarctions due to the risk of triggering more angina. However, through experience, I discovered that such patients actually have lower blood pressure when receiving the topiramate/phentermine combination, than when either drug is administered alone. These patients also have less angina and cardiac symptoms, which is an unexpected finding. Most cardiologists would never consider giving phentermine, alone or in combination with topiramate, for weight loss to patients with known coronary artery disease or angina.

For diabetic patients that are seeking weight loss, I have also been able to discontinue diabetes pills at the start of treatment with the topiramate/phentermine combination, and have consistently observed that patients ultimately have lower blood sugars and hemoglobin A1c levels than they did while on oral hypoglycemics. Insulin can often be discontinued by the 2nd or

3rd month of treatment with the topiramate/phentermine combination, and the patients have lower blood sugars and hemoglobin A1c levels that they did while on insulin. Again, these results are unexpected and not seen to this degree with any other weight loss medication.

11. There is no doubt in my mind that the treatment that I discovered using a combination of an anticonvulsant sulfamate derivative such as topiramate with a sympathomimetic agent such as phentermine is the best treatment by far than any that I have used in the past, including phen-fen. Many patients who previously used phen-fen have told me the topiramate/phentermine combination treatment was easier, better tolerated, had less side effects, and was more effective than phen-fen.

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 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 § 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 issuing thereon.

Respectfully submitted,

Date: 7/12/02 By: Thomas Najarian, M.D.

Declarant: Thomas Najarian

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