UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
CLARKSBURG DIVISION

CEPHALON, INC.,

Plaintiff,

v.

MYLAN PHARMACEUTICALS, INC., and MYLAN LABORATORIES, INC.,

Defendants.

Civil Action No. 1:03CV44

COMPLAINT

Plaintiff Cephalon, Inc. ("Cephalon"), by its attorneys, hereby alleges as follows for its Complaint against Mylan Pharmaceuticals, Inc. ("Mylan Pharmaceuticals") and Mylan Laboratories, Inc. ("Mylan Laboratories"):

Nature of the Action

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, 35 U.S.C. §§ 271 and 281. This action relates to an Abbreviated New Drug Application ("ANDA") filed by Mylan Pharmaceuticals with the United States Food and Drug Administration ("FDA") for approval to market a generic version of Cephalon's PROVIGIL® drug product.

Parties

2. Cephalon is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 145 Brandywine Parkway, West Chester, Pennsylvania.

3. Upon information and belief, Mylan Pharmaceuticals is a corporation organized and existing under the laws of the State of West Virginia, with its principal place of business at

781 Chestnut Ridge Road, Morgantown, West Virginia. Upon information and belief, Mylan Pharmaceuticals is a wholly-owned subsidiary of Mylan Laboratories.

4. Upon information and belief, Mylan Laboratories is a corporation organized and existing under the laws of the State of Pennsylvania, with its principal place of business at 130 Seventh Street, 1030 Century Building, Pittsburgh, Pennsylvania. Upon information and belief, Mylan Laboratories is doing business in this district directly, as well as through its wholly-owned subsidiary Mylan Pharmaceuticals. Upon information and belief, Mylan Laboratories has ultimate control over the activities of Mylan Pharmaceuticals. Hereinafter, Mylan Pharmaceuticals and Mylan Laboratories are referred to collectively as "Mylan."

Jurisdiction and Venue

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 1400(b), 2201 and 2202.

6. Each of Mylan Pharmaceuticals and Mylan Laboratories is subject to personal jurisdiction in this judicial district.

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

Cephalon's PROVIGIL® Patent

8. Cephalon is the owner by assignment of U.S. Reissue Patent No. RE37,516 ("the RE '516 Patent"), entitled "Acetamide Derivative Having Defined Particle Size," which the United States Patent and Trademark Office duly and legally issued on January 15, 2002. A true and correct copy of the RE '516 Patent is attached hereto as Exhibit A. The claims of the RE '516 Patent are valid and enforceable. Cephalon owns all right and title to the RE '516 Patent and has the right to sue for and obtain equitable relief and damages for infringement. The RE '516 Patent expires on October 6, 2014.

9. PROVIGIL® modafinil, which is covered by claims of the RE '516 Patent, is the commercial formulation of modafinil developed, manufactured and sold by Cephalon. PROVIGIL® was approved by the FDA on December 24, 1998, for treatment of excessive daytime sleepiness associated with narcolepsy. The FDA's official publication of approved drugs (the "Orange Book") includes PROVIGIL® listed together with the RE '516 Patent.

10. PROVIGIL® modafinil is further protected by marketing exclusivity under 21 U.S.C. § 355(j)(5)(D)(ii) until December 24, 2003, and by orphan drug exclusivity until December 24, 2005.

Infringement by Mylan

11. By letter dated February 12, 2003 (the "Mylan Notice Letter"), Mylan Pharmaceuticals notified Cephalon that Mylan Pharmaceuticals had submitted ANDA No. 76-594 (the "Mylan ANDA") to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking approval to engage in the commercial manufacture, use and sale of tablets containing 100 mg and 200 mg of modafinil (the "Mylan ANDA Modafinil Tablets"), a generic version of PROVIGIL® modafinil tablets, before the expiration date of the RE '516 Patent. Upon information and belief, Mylan Pharmaceuticals intends to engage in the commercial manufacture, use and sale of the Mylan ANDA Modafinil Tablets promptly upon receiving FDA approval to do so.

12. By filing ANDA No. 76-594, Mylan Pharmaceuticals has necessarily represented to the FDA that the Mylan ANDA Modafinil Tablets have the same active ingredient as PROVIGIL®, have the same route of administration, dosage form, and strengths as PROVIGIL®, are bioequivalent to PROVIGIL®, and have the same or substantially the same proposed labeling as PROVIGIL®.

13. In the Mylan Notice Letter, Mylan Pharmaceuticals notified Cephalon that its ANDA contained a "paragraph IV certification" that, in Mylan Pharmaceuticals' opinion, no valid claim of the RE '516 Patent will be infringed by the manufacture, use, offer for sale, or sale of the Mylan ANDA Modafinil Tablets.

14. Mylan Pharmaceuticals' submission of ANDA No. 76-594 to obtain approval to engage in the commercial manufacture, use, offer to sell or sale of the Mylan ANDA Modafinil Tablets, prior to the expiration of the RE '516 Patent, constitutes infringement of one or more of the valid claims of the RE '516 Patent under 35 U.S.C. § 271(e)(2)(A).

15. Mylan Pharmaceuticals' commercial manufacture, use, offer to sell or sale of the Mylan ANDA Modafinil Tablets, prior to the expiration of the RE '516 Patent, would constitute further acts of infringement of such patent under 35 U.S.C. § 271. Mylan Pharmaceuticals' filing of its ANDA, and Mylan Pharmaceuticals' intention to engage in the commercial manufacture, use, offer to sell or sale of the Mylan ANDA Modafinil Tablets upon receiving FDA approval, create an actual case or controversy with respect to infringement of the RE '516 Patent.

16. Upon FDA approval of the Mylan ANDA, Mylan Pharmaceuticals will infringe the RE '516 Patent by making, using, offering to sell, and selling the Mylan ANDA Modafinil Tablets in the United States, and by actively inducing and contributing to infringement by others, unless enjoined by this Court.

17. Upon information and belief, while the Mylan ANDA was filed in the name of Mylan Pharmaceuticals, it also was filed for the benefit of, and with the knowledge and approval of, Mylan Laboratories.

18. Upon information and belief, the officers and directors of Mylan Pharmaceuticals and Mylan Laboratories directed the preparation and filing of the Mylan ANDA.

19. Mylan Laboratories is liable for Mylan Pharmaceuticals' infringement of the RE '516 Patent because, upon information and belief, Mylan Laboratories caused or participated in, contributed to, aided, abetted, directed and induced the submission of the Mylan ANDA.

20. Cephalon will be substantially and irreparably damaged and harmed if Mylan's infringement is not enjoined. Cephalon does not have an adequate remedy at law.

21. This action is being brought before the expiration of forty-five days from the date Cephalon received the Mylan Notice Letter, which Cephalon received no earlier than February 19, 2003.

Prayer for Relief

WHEREFORE, Cephalon prays that this Court grant the following relief:

A. A declaration that the RE '516 Patent is valid and enforceable;

B. A declaration that a claim or claims of the RE '516 Patent are infringed by the Mylan ANDA Modafinil Tablets, that Mylan Pharmaceuticals' submission of its ANDA No. 76-594 is an act of infringement, and that Mylan's making, using, offering to sell, selling, or importing the Mylan ANDA Modafinil Tablets will infringe the RE '516 Patent;

C. A declaration that Mylan Laboratories is directly liable for Mylan Pharmaceuticals' infringement, and/or jointly and severally liable for inducing Mylan Pharmaceuticals' infringement;

D. An Order providing that the effective date of any approval of Mylan Pharmaceuticals' ANDA No. 76-594 shall be a date which is not earlier than the date of the expiration of the RE '516 Patent;

E. An Order permanently enjoining Mylan Pharmaceuticals, Mylan Laboratories and their affiliates and subsidiaries, and each of their officers, agents, servants and employees, from making, using, offering to sell, selling, or importing the Mylan ANDA Modafinil Tablets until after the date of the expiration of the RE '516 Patent;

F. Damages or other monetary relief to Cephalon if Mylan Pharmaceuticals or Mylan Laboratories engages in the commercial manufacture, use, offer to sell, sale, or importation of the Mylan ANDA Modafinil Tablets prior to the expiration of the RE '516 Patent;

G. Reasonable attorneys' fees, filing fees and reasonable costs of suit incurred by Cephalon in this action; and

H. Such further and other relief as this Court deems proper and just.

Dated: April 1, 2003

Respectfully submitted,

Cephalon, Inc.
By Counsel

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Jcf0559

EXHIBIT A

US00RE37516B1

(19) **United States**

(12) **Reissued Patent**

Grebow et al.

(10) **Patent Number: US RE37,516 E**

(45) **Date of Reissued Patent: Jan. 15, 2002**

(54) **ACETAMIDE DERIVATIVE HAVING DEFINED PARTICLE SIZE**

(75) Inventors: **Peter E. Grebow**, Penllyn, PA (US); **Vincent Corvari**, Nahua, NH (US); **David Stong**, Coatesville, PA (US)

(73) Assignee: **Cephalon, Inc.**, West Chester, PA (US)

(21) Appl. No.: **09/285,166**

(22) Filed: **Apr. 1, 1999**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,618,845**
Issued: **Apr. 8, 1997**
Appl. No.: **08/319,124**
Filed: **Oct. 6, 1994**

(51) **Int. Cl.**[7] **A61K 31/16**; A61K 9/14

(52) **U.S. Cl.** **514/618**; 424/489

(58) **Field of Search** 514/618; 424/489

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Primary Examiner—James H. Reamer

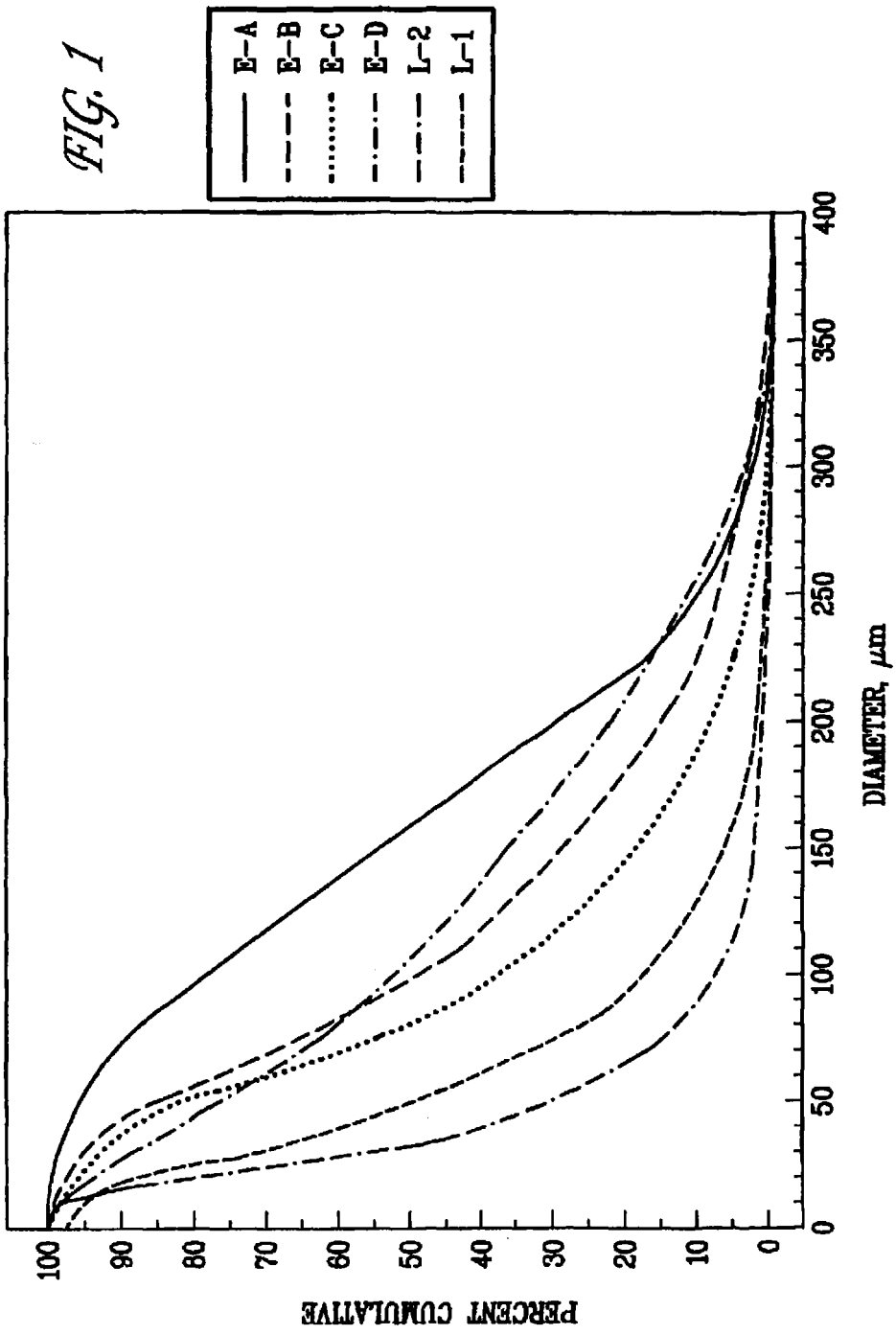
(74) *Attorney, Agent, or Firm*—Robert T. Hrubiec

(57) **ABSTRACT**

Pharmaceutical compositions comprising modafinil in the form of particles of defined size. The particle size of modafinil can have a significant effect on the potency and safety profile of the drug.

26 Claims, 7 Drawing Sheets

FIG. 1


E-A
E-B
E-C
E-D
L-2
L-1
PERCENT CUMULATIVE
100
90
80
70
60
50
40
30
20
10
0
DIAMETER, μm
0
50
100
150
200
250
300
350
400

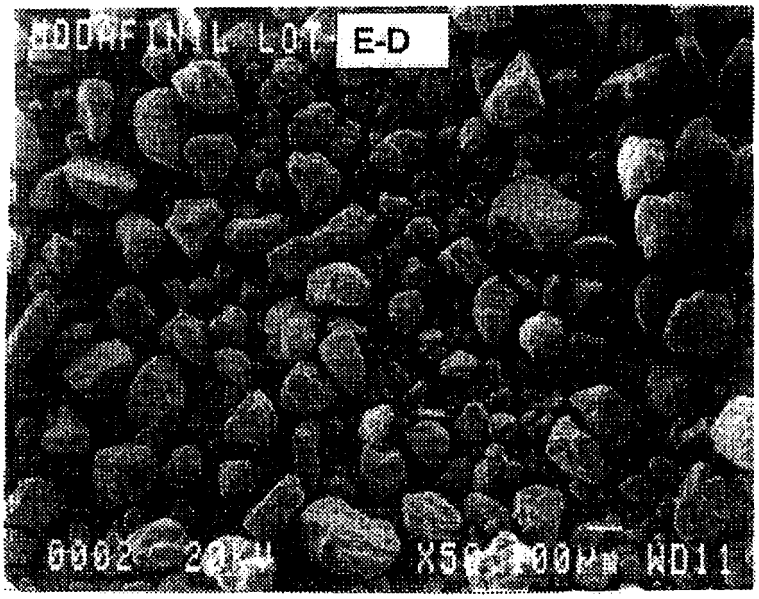


FIG. 2

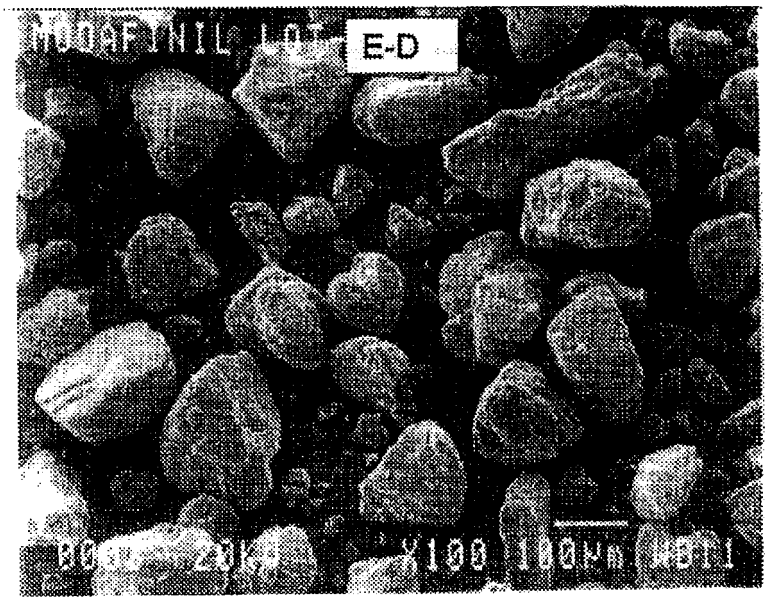


FIG. 3

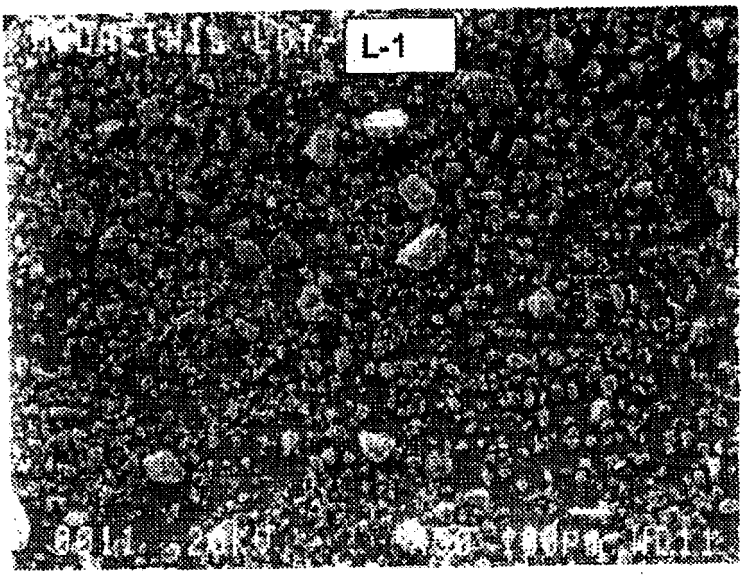


FIG. 4

FIG. 5

FIG. 6

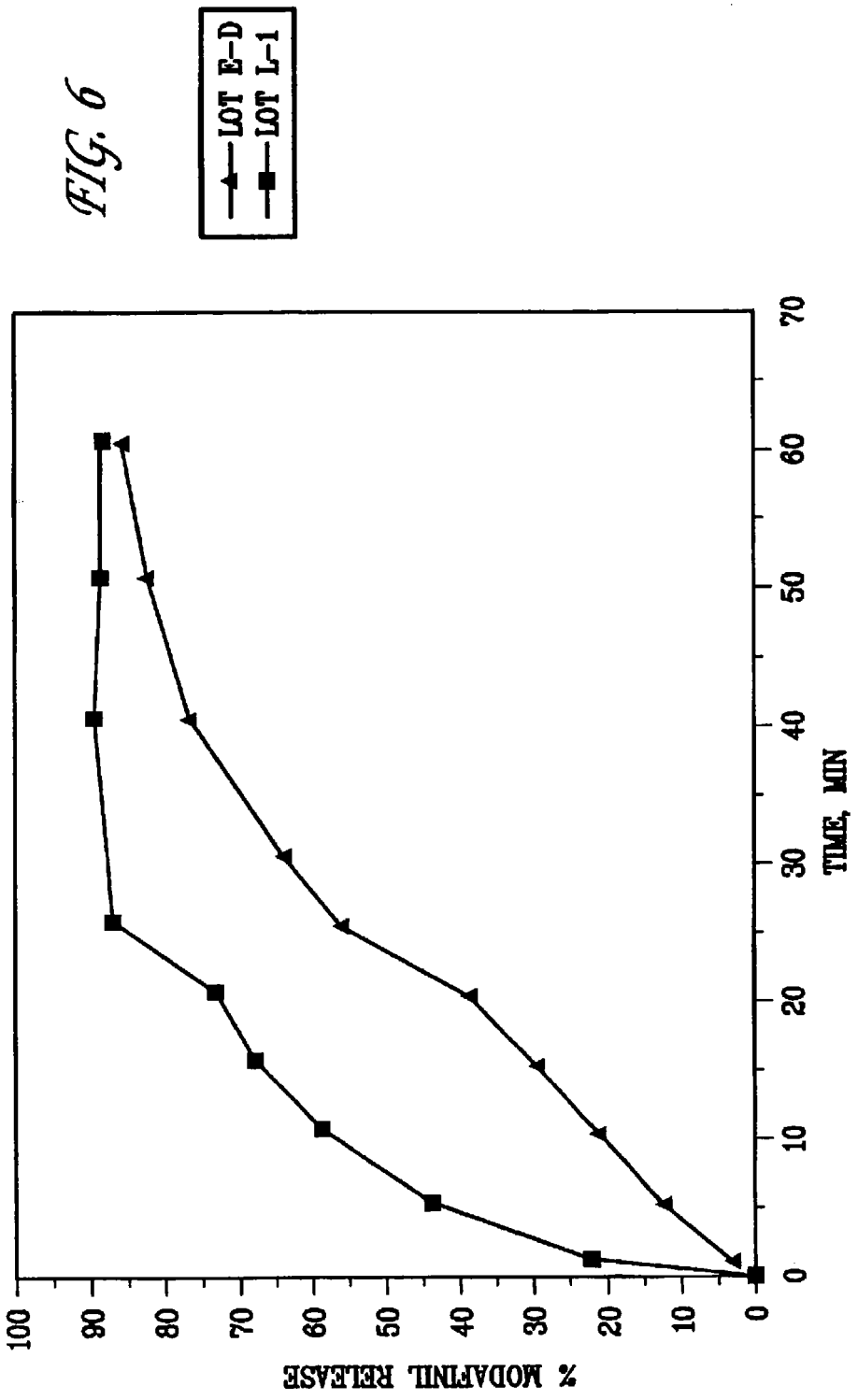
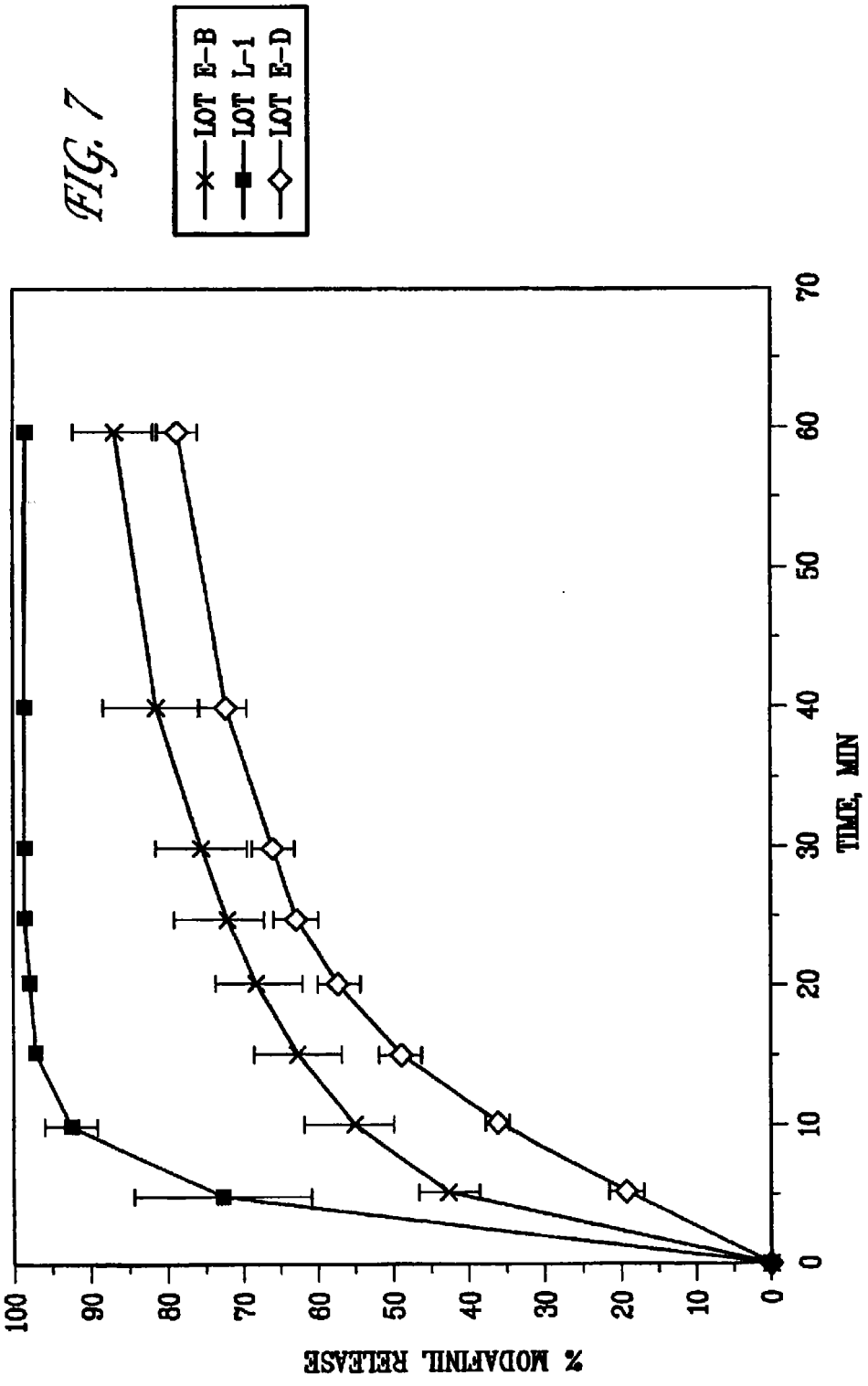

LOT E-D
LOT L-1
% MODAFINIL RELEASE
TIME, MIN
0
10
20
30
40
50
60
70
80
90
100

FIG. 7


LOT E-B
LOT L-1
LOT E-D
% MODAFINIL RELEASE
TIME, MIN
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10
20
30
40
50
60
70
80
90
100

FIG. 8

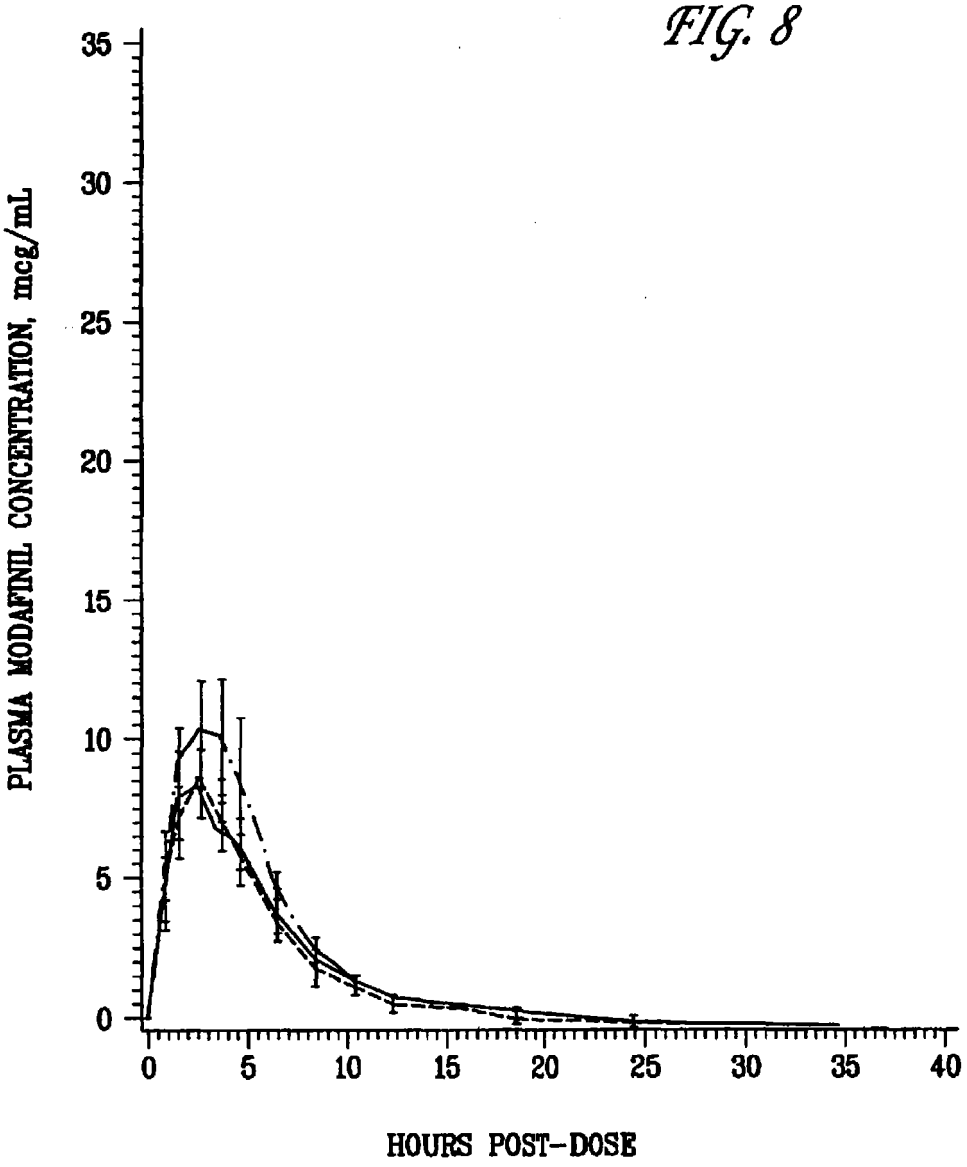
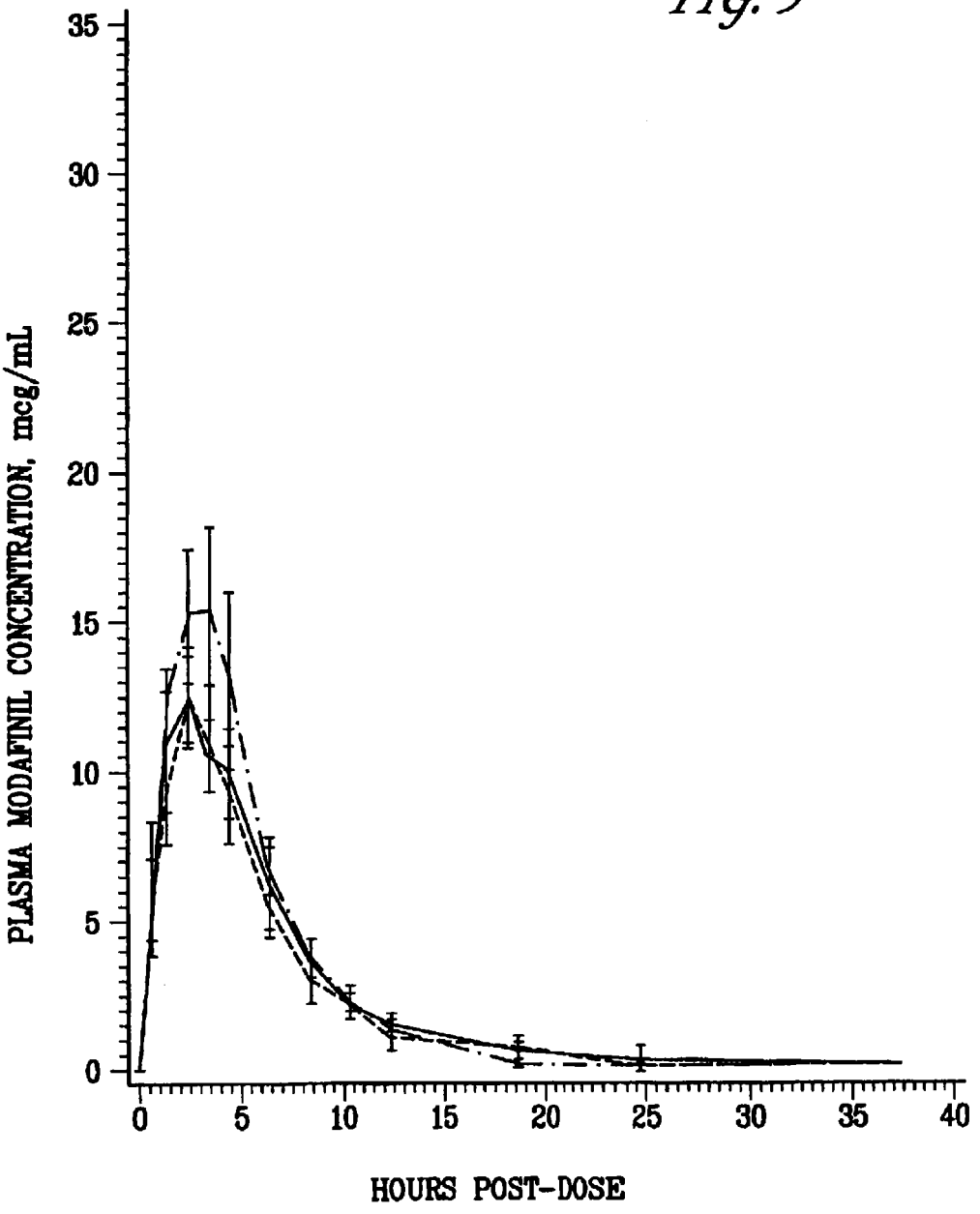

PLASMA MODAFINIL CONCENTRATION, mcg/mL
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
35
40
HOURS POST-DOSE

FIG. 9


PLASMA MODAFINIL CONCENTRATION, mcg/mL
0
5
10
15
20
25
30
35
0
5
10
15
20
25
30
35
40
HOURS POST-DOSE

ACETAMIDE DERIVATIVE HAVING DEFINED PARTICLE SIZE

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

BACKGROUND OF THE INVENTION

Publications cited in this document are incorporated herein by reference.

This invention relates to the acetamide derivative modafinil. Modafinil ($C_{15}H_{15}NO_2S$), is 2-(benzhydrylsulfinyl) acetamide, and is also known as 2-[(diphenylmethyl) sulfinyl]acetamide.

Modafinil has been described as presenting a "neuropsychopharmacological spectrum characterized by the presence of excitation with hyperactivity and of hypermotility, and by the absence of stereotypy (except in high doses) and of potentialisation of the effects of apomorphine and amphetamine" (U.S. Pat. No. 4,177,290; hereinafter the "'290 patent," which is incorporated herein by reference). A single administration of modafinil results in increased locomotor activity in mice and increased nocturnal activity in monkeys (Duteil et al., Eur. J. Pharmacol. 180:49 (1990)). The neuropsychopharmacological profile of modafinil has been distinguished from that of amphetamines (Saletu et al., Int. J. Clin. Pharm. Res. 9:183 (1989)). Modafinil is thought to modulate the central postsynaptic alpha$_1$-adrenergic receptor, without participation of the dopaminergic system (Duteil et al., supra). Modafinil has been successfully tested in humans for treatment of idiopathic hypersomnia and narcolepsy (Bastuji et al., Prog. Neuro-Psych. Biol. Psych. 12:695 (1988)).

Narcolepsy is a chronic disorder characterized by intermittent sleep attacks, persistent, excessive daytime sleepiness and abnormal rapid eye movement ("REM") sleep manifestations, such as sleep-onset REM periods, cataplexy, sleep paralysis and hypnagogic hallucinations, or both (Assoc. of Sleep Disorders Centers, Sleep 2:1 (1979)). Most patients with narcolepsy also have disrupted nocturnal sleep (Montplaisir, in Guilleminault et al. eds., Narcolepsy, Spectrum Pub., New York, pp. 43–56). Pathological somnolence, whether due to narcolepsy or other causes, is disabling and potentially dangerous. Causes of pathological somnolence, other than narcolepsy, include chronic sleep loss (Carskadon et al., Sleep, 5:S73 (1982); Carskadon et al., Psychophysiology, 18:107 (1981)); sleep apnea (Kryger et al., Principles and Practice of Sleep Medicine, W. B. Saunders Co., Philadelphia, Pa. (1989)); and other sleep disorders (International Classification of Sleep Disorders: Diagnostic and Coding Manual, American Sleep Disorder Association, Rochester, Minn. (1990)). Whether due to narcolepsy or other causes, pathological somnolence produces episodes of unintended sleep, reduced attention, and performance errors. Consequently, it is linked to a variety of transportation and industrial accidents (Mitler et al., Sleep 11:100 (1988)). A therapeutic agent that reduces or eliminates pathological somnolence would have important implications not only for individual patients, but also for public health and safety.

Other uses of modafinil have been presented. U.S. Pat. No. 5,180,745 discloses the use of modafinil for providing a neuroprotective effect in humans, and in particular for the treatment of Parkinson's disease. The levorotatory form of modafinil, i.e., (−)benzhydrylsulfinyl-acetamide, may have potential benefit for treatment of depression, hypersomnia and Alzheimer's disease (U.S. Pat. No. 4,927,855). European Published Application 547952 (published Jun. 23, 1993) discloses the use of modafinil as an anti-ischemic agent. European Published Application 594507 (published Apr. 27, 1994) discloses the use of modafinil to treat urinary incontinence.

SUMMARY OF THE INVENTION

Our invention discloses a pharmaceutical composition comprising modafinil in the form of particles of a defined size, and the use of such composition. We have discovered that the size of modafinil particles is important to the potency and safety profile of the drug.

"Particle," as used herein, refers to an aggregated physical unit of the acetamide compound, i.e., a piece or a grain of acetamide. For example, FIGS. 2–5 provide photographic representations of various modafinil particles from Lots E-D and L-1.

As used herein, the term "mean," when used in reference to the size of modafinil particles, refers to the sum of the size measurements of all measurable particles measured divided by the total number of particles measured. For example, for five measurable particles which could be measured, and were determined to have diameters of 20 microns, 23 microns, 20 microns, 35 microns and 20 microns, the mean diameter would be 23.6 microns. As used herein, the term "diameter" is a volumetric measurement based on the presumed spherical shape of modafinil particles.

As used herein, the term "median," when used in reference to the size of modafinil particles, indicates that about 50% of all measurable particles measured have a particle size less than the defined median particle size value, and that about 50% of all measurable particles measured have a particle size greater than the defined median particle size value. For example, for the five particle values listed above, the median diameter would be 20 microns.

As used herein, the term "mode," when used in reference to the size of modafinil particles, indicates the most frequently-occurring particle size value. For example, for the five particle values listed above, the mode diameter would be 20 microns.

As used herein, the term "percent cumulative," when used in reference to the size of modafinil particles, refers to an aggregate of the individual percent values for all measurable particles measured at specified diameters.

As used herein, "about" means plus or minus approximately ten percent of the indicated value, such that "about 20 microns" indicates approximately 18 to 22 microns. The size of the particle can be determined, e.g., by the methods provided below, and by conventional methods known to those of skill in the art.

In accordance with the invention disclosed herein, the mean particle size for a modafinil particle preferably ranges from about 2 microns to about 19 microns, more preferably from about 5 microns to about 18 microns, and most preferably from about 10 microns to about 17 microns.

In accordance with the invention disclosed herein, the median particle size for modafinil preferably ranges from about 2 microns to about 60 microns, more preferably from about 10 microns to 50 microns, and most preferably from about 20 microns to about 40 microns.

In accordance with the invention disclosed herein, the mode particle size for modafinil preferably ranges from about 2 microns to about 60 microns, more preferably from about 10 microns to about 50 microns, and most preferably from about 20 microns to about 40 microns.

We view the median measurement as having greater importance compared to the mode or mean values in that the median value provides an indication of the distribution of the particles measured in a given population. While not necessarily a limitation but rather an indicator of the consistency of the population measured, the ratio of median: mean: mode would ideally be 1:1:1; however, a ratio of median to mean of 1:2.50 to 1:0.50 is acceptable, and a ratio of median to mode of 1:2.50 to 1:0.50 is acceptable. Ideally, the standard deviation between the mean, median and mode measurements of a modafinil population would approach zero, indicating that every particle in the population measured was substantially identical or met the criteria for an ideal, normalized distribution. A standard deviation of less than about 25 between the mean, median and mode measurements is acceptable as an indication of the consistency of the population of the particles measured.

In accordance with the invention disclosed herein, it is preferable that not more than about 5% of the cumulative total (percent cumulative) of modafinil particles in any one dose provided to a mammal have particle sizes greater than about 200 microns; it is more preferable that not more than about 5% of the cumulative total (percent cumulative) of modafinil particles in any one dose provided to a mammal have particle sizes greater than about 190 microns; it is most preferable that not more than about 5% of the cumulative total (percent cumulative) of modafinil particles in any one dose provided to a mammal have particle sizes greater than about 180 microns. Thus, a "substantially homogeneous mixture" of modafinil particles, as utilized herein, refers to a mixture of modafinil particles in which at least about 95% of the particles in that mixture are less than a defined size.

The value ranges defined above are based upon measurements made utilizing technology and instruments developed by the Hiac/Royko Division of Pacific Scientific (11801 Tech Road, Silver Spring, Md. 20904, United States of America). As those in the art may appreciate, different instruments manufactured by different companies may provide different measurements for the same particles. For example, in a characteristic modafinil lot (Lot L-2), the mean, median, and mode particle measurements obtained using a Coulter Counter TA II sizing counter were 43, 31, and 29 microns, respectively. Using a Hiac/Royko Model 9064 sizing counter, the mean, median and mode particle measurements obtained for Lot L-2 were 18.75, 31.41 and 25.31 microns, respectively. These differences are presumably predicated upon the different approaches used in measuring particles of such diminutive sizes. Thus, the value ranges provided above are relative and are most preferably to be considered in view of utilization of instruments and operating systems manufactured by Hiac/Royko, for example, and preferably, the Hiac/Royko Model 9064 system sizing counter.

Modafinil particles of the invention can be in the form of a pharmacologically acceptable salt, e.g., an acidic or basic addition salt.

In another aspect, the invention features a method of altering a somnolent state, e.g., narcolepsy, idiopathic hypersomnia and related sleep disorders, using modafinil particles of a defined size. The method involves administering to a mammal a pharmaceutical composition comprising an effective amount of modafinil in the form of particles of a defined size.

"An effective amount", as used herein, is an amount of the pharmaceutical composition that is effective for treating a somnolent or somnolescent state, i.e., an amount of modafinil of a defined particle size that is able to reduce or eliminate the symptoms of a somnolescent state. An effective amount of a pharmaceutical composition of the invention is useful for enhancing alertness, or increasing regularity of sleep rhythms.

A "pharmaceutical composition", as used herein, means a medicament for use in treating a mammal that comprises modafinil of a defined particle size prepared in a manner that is appropriate for administration to a mammal. A pharmaceutical composition according to the invention may also, but does not of necessity, include a non-toxic pharmaceutically acceptable carrier.

The pharmaceutical composition of the invention can contain at least about 50 mg, preferably at least about 100 mg, or more preferably at least about 200 mg of modafinil having a particle size as defined above. The pharmaceutical composition preferably contains no more than about 700 mg; more preferably, no more than about 600 mg; and most preferably, no more than about 400 mg, of modafinil having a particle size as defined above.

Other features and advantages of the invention will be apparent from the following detailed description and from the claims.

DETAILED DESCRIPTION

We first briefly describe the drawings.

I. Drawings

FIG. **1** is a graph depicting particle size distributions for six lots of modafinil: Lots L-1, L-2, E-A, E-B, E-C and E-D.

FIG. **2** is a scanning electron micrograph of a sample of modafinil Lot E-D at 50× magnification.

FIG. **3** is a scanning electron micrograph of a sample of modafinil Lot E-D at 100× magnification.

FIG. **4** is a scanning electron micrograph of a sample of modafinil Lot L-1 at 50× magnification.

FIG. **5** is a scanning electron micrograph of a sample of modafinil Lot L-1 at 100× magnification.

FIG. **6** is a graph depicting the dissolution rate of modafinil particles from Lot E-D (median particle size 94.05 μm) and Lot L-1 (median particle size 50.18 μm).

FIG. **7** is a graph depicting the dissolution rate of modafinil particles from Lot E-B (median particle size 89.10 μm), Lot E-D (median particle size 94.05 μm) and Lot L-1 (median particle size 50.18 μm).

FIG. **8** is a graph depicting mean plasma concentration of modafinil in dogs following single oral doses of modafinil from lots with different particle sizes.

FIG. **9** is a graph depicting mean plasma concentration of modafinil equivalents, i.e., modafinil and modafinil acid metabolite, in dogs, following single oral doses of modafinil from lots with different particle sizes.

II. The Invention

The invention results from our discovery that the particle size, and the consistency of the particle size, of modafinil can have a significant effect on its potency and safety profile.

The first human trials for the use of modafinil to treat narcolepsy took place outside of the United States of America. The modafinil used in the initial studies was prepared in non-commercial scale lots (referred to herein as "early" or "E" lots). Pursuant to our discovery of the present invention, it was observed that the early lots had a median particle size of between 80 microns ("μm") and 150 μm. In the initial safety studies conducted outside of the United States, early lot modafinil was administered to humans without reports of clinically significant adverse events in acute administration.

TABLE 2

GROUP	NUMBER OF DOGS	WEEK	BULK DRUG LOT AND MEDIAN PARTICLE SIZE
1	3	1	E-D (94.05 μm)
		2	L-1 (50.18 μm)
		3	E-B (89.10 μm)
2	3	1	L-1 (50.18 μm)
		2	E-B (89.10 μm)
		3	E-D (94.05 μm)
3	3	1	E-B (89.10 μm)
		2	E-D (94.05 μm)
		3	L-1 (50.18 μm)

After each weekly dose, blood samples (2 ml) were drawn from all animals by venepuncture predose (within one hour of dosing), and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, and 36 hours post-dose. Blood samples were collected in heparinized (lithium heparin) test tubes and centrifuged at 2,500 to 3,000 rpm. The plasma was drawn off with a glass pipette, and stored frozen (−20° C.) until analyzed. The plasma concentration of modafinil, and its acid and sulfone metabolites were simultaneously determined by high-pressure liquid chromatography, according to the method of Moachon et al. (J. Chromatag. B 654:91 (1994)).

Mean plasma modafinil levels in the nine dogs, at 0 to 36 hours after modafinil administration, are depicted in FIG. 8. With "small" particles (Lot L-1), the plasma modafinil concentration peaked at 10 μg/ml. In contrast, with "larger" particles (Lots E-D or E-B), the plasma modafinil concentration peaked at 8 μg/ml. Thus, the modafinil having a median particle size of 50.18 μm resulted in a higher peak plasma concentration than that obtained with the same dose of modafinil administered in the form of larger particles. Similar results were observed regarding the acid metabolite of modafinil, 2-benzhydrylsulfinylacetic acid as depicted in FIG. 9.

These results implicated the consequences of different particle sizes and the importance of controlling modafinil particle size. By controlling the particle size, safety concerns can be addressed. For example, a non-homogenous mixture of modafinil particle sizes may not provide consistent potency nor avoid undesired fluctuations in plasma modafinil concentrations; such fluctuations can lead to undesired and unexpected events. Moreover, the use of modafinil particles having a defined size is more efficient because a given plasma modafinil concentration can be achieved at a lower oral dose.

After the discrepancy between the foreign and first United States studies was resolved and determined to be related to the differences in particle sizes, a second Phase I study was conducted in the United States, to further determine the clinical safety, tolerance and pharmacokinetic properties of modafinil having a particle size as defined. The second study involved normal young males and an experimental design similar to the first United States study (described above). In the second study, all subjects began at 200 mg/day using modafinil from Lots L-1 or L-2. Dosage was then titrated, in 200 mg/day increments, up to the target dose. The results of this study suggested that 600 mg/day was the maximum tolerable dose ("MTD") of modafinil, with 800 mg/day being the minimum intolerable dose.

IX. Methods of Preparing Modafinil Having Defined Size

Modafinil and modafinil-related compounds can be prepared by conventional methods. Methods for preparing modafinil and modafinil-related compounds appears in the '290 patent. Modafinil of the particle size defined herein may be obtained by a variety of approaches utilizing conventional methods, e.g., the methods disclosed in the '290 patent, and then subjecting the modafinil of undefined particle size to conventional methods of milling and sieving. Methods for comminution (i.e., the mechanical process of reducing the size of particles or aggregates) are known to those in the art. Examples are provided in O'Conner et al. Chpt. 88, Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co., Easton, Pa. (1990). Following comminution, the particles can be separated into a series of sieve cuts by passing the particles downward through an agitated vertical stack of sieves of decreasing mesh sizes and collecting the granules retained on each sieve or in the bottom pan. Particles which fall outside of a desired range can again be subjected to milling and sieving.

X. Formulation and Administration

An appropriate dosage for modafinil having a defined particle size is between about 50 mg and about 700 mg of modafinil.

The pharmaceutical composition described herein is most preferably administered orally in the form of a vehicle such as a tablet, capsule, powder, pill, liquid/suspension or emulsion. The administration vehicle may comprise a pharmaceutically-acceptable carrier. The carrier may comprise agents that aid solubility, absorption, flavor, color or texture of the vehicle or its contents. Topical administration via an epidermal patch or the like, or administration via direct injection of the drug, is also acceptable.

A vehicle of the invention can include ±10–15% of the modafinil particle, due to factors such as vehicle manufacturing tolerances and expected shelf life of the modafinil. For example, a vehicle labeled as containing 50 mg can be initially prepared with, e.g., 55 or 58 mg of modafinil, with the expectation that after one month to two years of storage, the active amount of modafinil therein has decreased. Vehicles prepared with such adjustments in order to compensate for the expected degradation of the drug fall within the scope of the invention.

While the invention has been described in considerable detail, the invention disclosed herein is not to be limited to the actual description, but is to be afforded the full scope of the appended claims and all equivalents thereto. Although the specific examples presented herein are directed to the use of modafinil of a defined particle size in the mediation of narcolepsy, other uses of modafinil (e.g., for treatment of Parkinson's disease, urinary incontinence, Alzheimer's disorder, etc.) have been presented in the art, and those utilities are appropriate in conjunction with the invention as disclosed herein.

What is claimed is:

1. A pharmaceutical composition comprising a substantially homogeneous mixture of modafinil particles, wherein at least about 95% of the cumulative total of modafinil particles in said composition have a diameter of less than about 200 microns (μm).

2. The composition of claim 1 wherein said particles have a median diameter range of between about 2μm and about 60 μm.

3. The composition of claim 1, wherein said composition comprises between about 50 milligrams and about 700 milligrams of said modafinil.

4. A method of altering the somnolent state of a mammal, said method comprising administering an effective amount of the composition of claim 1 to said mammal.

5. The method of claim 4, wherein said somnolent state is narcolepsy.

6. The method of claim 4, wherein said effective amount comprises between about 50 milligrams/day and about 700 milligrams/day of said composition.