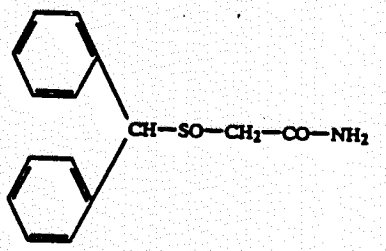
BEST POSSIBLE COPY

LEVOROTATORY ISOMER OF BENZHYDRYLSULFINYL DERIVATIVES

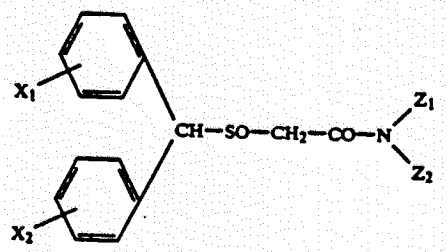
The present invention relates to the levorotatory derivative of benzhydrylsulfinylacetamide, the method for its preparation and its use in therapy, especially as an antidepressant and stimulant for the central nervous system (CNS), the said derivative being useful in particular in the treatment of hypersomnia on account of its arousing effects.

It is known that French Pat. No. 78 05 510 (publication No. Fr-B-2 385 693) describes the racemate (±)-benzhydrylsulfinylacetamide, which has the code number CRL 40 476 and the following structural formula:



as a product (see Example 1 of the said French patent) and as stimulant for the central nervous system (CNS).

It is also known that, in Patent Document EP-A-No. 0 097 071, the neuropsychopharmacological properties of the racemate were compared with those of the analogs of the formula:



in which:

X_1 and X_2, which can be identical or different, each represent, H, Cl or F,

Z_1 represents CH_3, CH_2Ch_3, $CH(CH_3)_3$, it also being possible for Z_1 to represent a hydrogen atom when at least one of the symbols X_1 and X_2 is different from H, and

Z_2 represents H, it being possible for NZ_1Z_2, considered together, to represent a piperidino or morpholino group,

which act on the CNS as sedatives in some cases and as stimulants in others (see especially Table I on page 3 and Table IV on page 4 of the said European patent document).

It has now been found that the levorotatory compound (−)-benzhydrylsulfinylacetamide (Code no.: CRL 40 982) has valuable therapeutic properties compared with the racemate (±)-benzhydrylsulfinylacetamide (Code no.: CRL 40 476) and with the dextrorotatory compound (+)-benzhydrylsulfinylacetamide (Code no.: CRL 40 983). Surprisingly, it has been found that the metabolism of the levorotatory compound in the organism is different form that of the racemate and the dextrorotatory compound and that the levorotatory compound is particularly valuable in the treatment of hypersomnia and Alzheimer's disease.

According to the invention, a novel industrial product is recommended which is useful in therapy and belongs to the family of the benzylhydrylsulfinyl derivatives, the said product being (−)-benzhydrylsulfinylacetamide.

This levorotatory compound cannot be prepared by isolation from the corresponding racemic amide. However, it can be prepared by chemical synthesis from a precursor of the amide, according to a method known per se, by the application of conventional reaction mechanisms.

The method of preparation recommended according to the invention consists in:

(1°) reacting (±)-benzhydrylsulfinylacetic acid with (−)-α-methylbenzylamine to give the (−)-benzhydrylsulfinylacetate of (−)-α-methylbenzylamine (the reaction advantageously being carried out in the presence of a small excess of amine relative to the stoichiometric conditions, and more particularly with a molar ratio amine/acid of between 1.02/1 and 1/15/1 and preferably of between 1.05/1 and 1.10/1),

(2°) converting the resulting (−)-benzhydrylsulfinylacetate salt of (−)-α-methylbenzylamine to (−)-benzhydrylsulfinylacetic acid [the conversion advantageously being carried out by hydrolysis in an acid medium, the solvent being warm water (especially water at 30°–45° C.], and

(3°) subjecting the resulting (−)-benzhydrylsulfinylacetic acid to an amidation reaction with gaseous ammonia.

The amidation of stage (3°) is advantageously carried out in 2 steps, namely:

(3a) esterification of the (−)-benzhydrylsulfinylacetic acid to a lower alkyl (−)-benzyldrylsulfinylacetate [the lower alkyl being C_1–C_3, especially isopropyl, ethyl or methyl (preferably ethyl and particularly preferably methyl)], followed by

(3b) transamidation of the resulting lower alkyl (−)-benzhydrylsulfinlacetate with NH_3 (the transamidation reaction preferably being carried out in a lower alcohol and particularly preferably in the alcohol corresponding to the alkyl group of the ester obtained in stage 3a), a stream of NH_3 being passed into the reaction medium).

(±)-Benzyhydrylsulfinylacetic acid is a known substance which is described as synthesis intermediate in Patent Document FR-B-No. 2 326 181 (m.p. (inst.) = 164°–165° C.).

According to the invention, a therapeutic composition is recommended which contains (−)-benzhydrylsulfinylacetamide as the active ingredient, in association with a physiologically acceptable excipient. Of course, in a composition of this type, the said (−)-benzhydrylsulfinylacetamide is present in a pharmaceutically effective amount.

It is also recommended to use this levorotatory compound to obtain, on the one hand, an arousing drug to be used in human therapy for hypersomnia, and, on the other hand, a stimulating drug, and in particular a drug for inhibiting aphasia and ideomotor apraxia, to be used in therapy for Alzheimer's disease.

Further advantages and characteristics of the invention will be understood more clearly from the following

BEST POSSIBLE COPY

description of (i) preparation examples and (ii) results of comparative neurophyschopharmacological tests. These data, which in no way imply a limitation, are given by way of illustration.

PREPARATION I

Preparation of (−)-benzhydrylsulfinylacetamide

(Example 1; Code no.: CRL 40 982)

(a) (−)-Benzhydrylsulfinylacetate of (−)-α-methylbenzylamine

13 g (0.108 mol) of (−)-α-methylbenzylamine are added to a suspension of 27.4 g (0.1 mol) of (±)-benzhydrylsulfinylacetic acid (m.p. (inst.)=164°-165° C.; Code no.: CRL 40 467) in 500 ml of water; the mixture is filtered hot, the filtrate is cooled and the product is filtered off and recrystallized twice from 300 ml of water to give 17 g (yield: 42%) of the (−)-benzhydrylsulfinylacetate of (−)-α-methylbenzylamine. M.p. (inst.)=148°-150° C.

(b) (−)-Benzhydrylsulfinylacetic acid

the (−)-benzhydrylsulfinylacetate of (−)-α-methylbenzylamine (17 g) obtained in this way is dissolved in 800 ml of warm water (30°-40° C.) and then acidified with 7 ml of concentrated hydrochloric acid (12N HCl, d=1.19 g/cm³). The mixture is filtered cold and the precipitate is washed with water and dried to give the expected (−)-benzhydrylsulfinylacetic acid with a yield of about 100%.

M.p. (inst.)=185°-188° C.

$\alpha_D^{20°C}=-35°$ (in a 1% solution in CH_3OH).

(c) Methyl (−)-benzhydrylsulfinylacetate

A suspension of 16.45 g (0.06 mol) of (−)-benzhydrylsulfinylacetic acid in 300 ml of water is treated at 20° C. with 16.8 g (0.2 mol) of sodium bicarbonate and 18.8 ml (0.21 mol) of methyls sulfate, with stirring, the mixture is stirred for 16 to 18 hours at 20° C. and filtered and the material on the filter is washed with water and dried to give methyl (−)-benzhydrylsulfinylacetate with a yield of 85%.

M.p. (inst.)=109°-110° C.

$\alpha_D^{20°C}=-22.5°$ (in a 4% solution in CH_3OH).

(d) CRL 40 982

A dry stream of NH_3 gas is passed at room temperature into a solution of 100 ml of methanol containing 8.6 g (0.03 mol) of methyl (−)-benzhydrylsulfinylacetate. NH_3 introduced in this way is reacted with the solution for 5 h, with stirring. The methanol is evaporated off, the evaporation residue is taken up in ether and the product is filtered off and recrystallized from ethanol to give CRL 40 982 with an overall yield of 32%. This product is in the form of white crystals which are soluble in alcohols and acetone and insoluble in water and ether.

M.p. (inst.)=153°-154° C.

$\alpha_D^{20°C}=-20°$ (in a 2% solution in CH_3OH),

PREPARATION II

Preparation of (+)-benzhydrylsulfinylacetamide

(Comparison product CP1; Code no.: CRL 40 983)

The following are obtained successively using the procedure indicated in Preparation I above but replacing the (−)-α-methylbenzylamine with (+)-α-methylbenzylamine.

(a) the (+)-benzhydrylsulfinylacetate of (+)-α-methylbenzylamine;

M.p. (inst.)=148°-150 C.;

(b) (+)-benzhydrylsulfinylacetic acid;

M.p. (inst.)=190°-191° C.,

$\alpha_D^{20°C}=+45°$ (in a 1% solution in CH_3OH);

(c) methyl (+)-benzylhydrylsulfinylacetate;

M.p. (inst.)=109°-110° C.,

$\alpha_D^{20°C}=+22.2°$ (in a 4% solution in CH_3OH);

and then

(d) CRL 40 983;

M.p. (inst.)=153°-154° C.,

$\alpha_D^{20°C}=+22°$ (in a 2% solution in CH_3OH).

The comparative tests which were undertaken with the levorotatory derivative according to the invention (Ex. 1; Code no.: CRL 40 982), the dextrorotatory derivative (CP1; Code no.: CRL 40 983) and the corresponding racemate (CP2; Code no.: CRL 40 476) have been summarized below. Unless indicated otherwise, the 3 products studied in these tests were administered intraperitoneally as a suspension in an aqueous solution of gum arabic, in a volume of 20 ml/kg to male mice and in a volume of 5 ml/kg to male rats.

A—TOXICITY

In male mice, the LD_0 (maximum non-lethal dose) by intraperitoneal administration is found to be greater than or equal to 512 mg/kg for the dextrorotatory compound and the racemate, whereas the LD_{30} of the levorotatory compound is of the order of about 512 mg/kg.

In summary, CRL 40 982 is more toxic than CRL 40 983 (CP1) and CRL 40 476 (CP2). The fact that the toxicity of CRL 40 982 is greater than that of the other two products does not present a problem since the levorotatory compound still has a sufficiently wide useful range of non-lethal concentrations. Here, the fact that CRL 40 982 is more toxic than the other two products indicates that it is more active.

B—BEHAVIOR IN RATS

In male mice, CRL 40 982, CRL 40 983 and CRL 40 476 have stimulant effects; in male rats, on the other hand, it is found that CRL 40 982 and CRL 40 983 do not have stimulant effects while the racemate (CRL 40 476) (i) is a stimulant and (ii) has a mydriatic action at all the doses used, the levorotatory and dextrorotatory isomers being devoid of this mydriatic action when administered on their own:

at a dose of 128 mg/kg, CRL 40 476 causes excitation with an increase in the fear ration for 2 h, exophthalmos for 1 h and mydriasis for 1 for 2 h;

at a dose of 32 mg/kg, CRL 40 476 causes excitation (transient, lasting 0.5 h) with an increase in the fear reaction for 1 h, exophthalmos for 0.5-1 h and mydriasis for 1-2 h;

at a dose of 8 mg/kg, CRL 40 476 causes exophthalmos for 0.5-1 h and mydriasis for 0.5 h;

at a dose of 2 mg/kg, CRL 40 476 induces transient mydriasis appearing 1 h after administration, whereas

at a doses of 64 mg/kg, 16 mg/kg, 4 mg/kg and 1 mg/kg, CRL 40 982 and CRL 40 983 cause behavior, reactivities and variations in the rectal temperature and pupil diameter which are substantially comparable to those of the control group.

C—MOTOR ACTIVITY IN MICE

The mice (6 per dose, 18 control animals) receive CRL 40 476, CRL 40 982 or CRL 40 983 four hours before being placed in an actimeter, where their motility is recorded for 30 minutes. It is found that, at doses of 128 mg/kg and to a lesser extent 64 mg/kg, the three substances used cause an increase in the motor activity four hours after their administration. However, the hyperactivity induced by CRL 40 982 and CRL 40 983

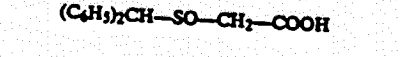
BEST POSSIBLE COPY

reaches a level and a degree of statistical significance which are greater than those due to CRL 40 476, especially at the highest dose used (128 mg/kg).

In summary, under the experimental conditions (intraperitoneal administration of the substances four hours before the test), CRL 40 982 shows a stimulant effect equal in intensity to that observed with CRL 40 983, while the hyperactivity induced by CRL 40 476 is less than that obtained with either CRL 40 982 or CRL 40 983.

D—PHARMACOKINETIC STUDY

In the organism, CRL 40 476 is partially converted to (±)-benzhydrylsulfinylacetic acid (CRL 40 467) of the structural formula:



$$(C_6H_5)_2CH—SO—CH_2—COOH$$

which is used as the starting material for the synthesis of the optical isomers CRL 40 982 and CRL 40 983.

Now, this metabolite is found to be inactive. In fact, CRL 40 467, administered intraperitoneally to male mice at doses of 1024 mg/kg, 512 mg/kg, 256 mg/kg, 128 mg/kg and 64 mg/kg, induces the appearance of brief sedation (with a duration less than or equal to about 50–60 minutes) and does not cause the death of any of the animals treated. Its neuropsychopharmacological study did not reveal any psychotropic activity.

to distinguish CRL 40 982 from the racemic and dextrorotatory compounds, a kinetic study of the metabolism was undertaken on dogs (group of four animals). In a randomized crossover procedure, each animal received the following at the rate of one oral administration per week: 2 administrations of CRL 40 476 (for assessment of the variations within individuals), 1 administration of CRL 40 982 and 1 administration of CRL 40 983. Following each of these administrations, the kinetics of the CRL 40 476 and CRL 40 467 present in the plasma were determined (without looking to see whether these two products were in the racemic, levorotatory and/or dextrorotatory form, because of the difficulties associated with determining the optical rotation of each of the optical isomers in a biological medium).

The dose administered for each of the test substances CRL 40 476, CRL 40 982 and CRL 40 983 was 30 mg/kg.

After administration of CRL 40 476, the said CRL 40 476 and its metabolite, CRL 40 467, are found in the plasma.

After the administration of CRL 40 982, the following are found in the plasma: the said CRL 40 982, which will be characterized and determined as being CRL 40 476 by way of convenience, in view of what has been said above, and a metabolite which will be characterized and determined as being CRL 40 467.

Likewise, after administration of CRL 40 983, the 2 corresponding products in the plasma will be characterized and determined as being CRL 40 476 and CRL 40 467.

The curves of the plasma concentrations of the said CRL 40 476 and CRL 40 467 as a function of time are plotted from time T=2 to time T=+9 h after administration of the CRL 40 476, CRL 40 982 and CRL 40 983. The areas under the curves (AUC_{0+9h}) are then calculated. The results obtained are recorded in Table I below. They show this:

(a) after administration of CRL 40 476 and CRL 40 983, the AUC_{0+9h} of CRL 40 476 are not statistically different, whereas, after administration of CRL 40 982, the AUC_{0+9h} of CRL 40 476 is approximately twice the AUC_{0+9h} of CRL 40 476 which each result from the administration of CRL 40 476 and CRL 40 476 and CRL 40 983; and

(b) the quantity of CRL 40 467 produced after administration of CRL 40 983 is very large (83.12 $mg.l^{-1}.h$), whereas the quantity produced after administration of CRL 40 982 is very small (8.69 $mg.l^{-1}.h$).

The value of CRL 40 982 according to the invention is in the fact that only a small proportion of this product is converted to inactive CRL 40 467, whereas a very high proportion of the corresponding dextrorotatory derivative is metabolized to CRL 40 467. In summary, the levorotatory compound CRL 40 982 has a better bioavailability than the racemic compound CRL 40 476 and the dextrorotatory compound CRL 40 983, in view of the small quantity of inactive metabolite which it produces in the organism.

These pharmacokinetic results were confirmed on rabbits and mice. An immunostimulant effect was also observed in vitro for CRL 40 982.

E—CLINICAL TRIALS

In human clinical trials, it was found that the elimination half-life of CRL 40 982 is relatively long (about 10 h), making it possible to obtain good results on adults with 1 to 2 administrations per day.

In the course of the clinical trials, CRL 40 982 was found to act in the short term as a purely hypnogenic, antiarousing substance and in the long term as an arousing substance useful for hypersomnia. Furthermore, in both the short and long term, CRL 40 982 was shown to be particularly active towards the symptoms of dementia and loss of memory (especially in the elderly).

Administered once or twice a day in the form of tablets or gelatin capsules each containing 50 to 100 mg of CRL 40 982, this product has a different stimulant neuropsychopharmacological profile from that of the amphetamines and tricyclic antidepressants and is useful of depressions, hypersomia and in particular Alzheimer's disease (improvement of the symptoms of dementia, memory disorders, aphasia and ideomotor apraxia).

BEST POSSIBLE COPY

TABLE I

PHARMACOKINETIC STUDY ON DOGS
MEASURMENT OF THE AREAS UNDER THE CURVES ($AUC_0^{+\infty}$)

Product administered	Code no.	$AUC_0^{+\infty}$ CRL 40 476 (a)		$AUC_0^{+\infty}$ CRL 40 467 (a)	
CP2	CRL 40 476	46.76 ± 6.95	**	35.12 ± 6.93	**
Ex. 1	CRL 40 982	97.22 ± 12.58	* n.s.	8.69 ± 1.22	** *
CP1	CRL 40 983	50.94 ± 8.77		83.12 ± 21.66	

Notes
(a) in $mg.l^{-1}.h$
* statistically significant difference ($p < 0.1$)
** statistically very significant difference ($p < 0.01$)
n.s. statistically non-significant difference

What is claimed is:

1. (−)-Benzhydrylsulfinylacetamide.

2. A method for the treatment of hypersomnia, which comprises administering, to a patient in need of such a treatment, an effective amount of a pharmaceutical composition consisting essentially of (−)-benzhydrylsulfinylacetamide as an arousing agent.

3. A method for the treatment of Alzheimer's disease, which comprises administering, to a patient in need of such a treatment, an effective amount of a pharmaceutical composition consisting essentially of (−)-benzylhydrylsulfinylacetamide as a central nervous system stimulant.

4. A therapeutic composition comprising an amount (−)-benzhydrylsulfinylacetamide in combination with a physiologically acceptable excipient effective to serve as an arousing agent.

5. A therapeutic composition comprising an amount effective as a central nervous system stimulant of (−)-benzhydrylsulfinylacetamide in combination with a physiologically acceptable excipient.

6. A pharmaceutical composition useful in therapy as a central nervous system stimulant consisting essentially of (−)-benzhydrylsulfinylacetamide in combination with a physiologically acceptable medium.

• • • • •

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

January 4, 1999

Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380-4245

Attention: Paul M. Kirsch
Director, Regulatory Affairs

Dear Mr. Kirsch:

Reference is made to your orphan product Provigil (modafinal), which was designated an orphan product pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 360bb) on March 15, 1993 [redacted] for the treatment of excessive daytime sleepiness in narcolepsy.

This letter is to inform you that as the first sponsor of Provigil to obtain marketing approval for this indication, you are entitled to seven years of exclusive marketing approval pursuant to Section 527 of the FFDCA (21 U.S.C. § 360cc) for the use of Provigil to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. The exclusive seven year approval period began on December 24, 1998, the date of approval of your new drug application (NDA 20-717).

Please note that holders of exclusivity for approved orphan products are required to assure the availability of sufficient quantities of an orphan drug to meet the needs of patients. Failure to do so could result in the withdrawal of the product's exclusive approval [21 CFR 316.36(b)].

Thank you for your efforts in developing Provigil for the treatment of narcolepsy. The whole premise of the Orphan Drug Act and program is based on the realization that the resources and commitment devoted to the development of products for "orphan" populations may not provide financial returns to their sponsors. It is with genuine gratitude that we recognize your efforts.

Sincerely yours,

[redacted] /S/

Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

BEST POSSIBLE COPY

Exclusivity Summary Form

(Modified: October 14, 1998)

EXCLUSIVITY SUMMARY FOR NDA # 20-717 **SUPPL #** _____

Trade Name: Provigil **Generic Name:** modafinil

Applicant Name: Cephalon, Inc. **HFD #** 120

Approval Date If Known: _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES/ ✓ **/ NO /** ___ **/**

b) Is it an effectiveness supplement?

YES / ___ **/ NO /** ✓ **/**

If yes, what type? (SE1, SE2, etc.) Ø

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / ✓ **/ NO /** ___ **/**

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Ø

Form OGD-011347 Revised 8/27/97
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES / ✓ **/ NO /** ___ **/**

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 yr. / 7 yr. (orphan)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / ___ **/ NO /** ✓ **/**

BEST POSSIBLE COPY

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? **(Rx to OTC switches should be answered NO - please indicate as such)**

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

BEST POSSIBLE COPY

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability

BEST POSSIBLE COPY

studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

BEST POSSIBLE COPY

interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/

Signature [redacted] ***ate:*** 12/11/98

Title: Project Manager

Signature of Office/Division Director

Signature: ***Date:***

cc: Original NDA Division File HFD-93 Mary Ann Holovac

Previous Page

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20717 **Trade Name:** PROVIGIL (MODAFINIL) 100/200MG TABLETS

Supplement Number: **Generic Name:** MODAFINIL

Supplement Type: **Dosage Form:** TAB

Regulatory Action: AP **Proposed Indication:** NARCOLEPSY

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? No

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ANNA MARIE HOMONNAY-WEIKEL

/S/ [redacted]
Signature

12/11/98
Date

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

Debarment Certification Under the Generic Drug Enforcement Act of 1992

Cephalon, Inc, certifies that it did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306 (a) or (b)], in connection with this new drug application.

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

MEMORANDUM

DATE: December 17, 1998

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-717

SUBJECT: Supervisory Review of Sponsor's Response to Approvable Letter for NDA 20-717, for the Use of Modafinil in Patients with Narcolepsy

BACKGROUND

On 12/29/97, the Agency issued an Approvable letter to Cephalon, Inc., sponsor of NDA 20-717, for the use of modafinil in patients with narcolepsy. That letter included requests for the following information:

Clinical

1) A complete accounting of the exact number of patients exposed to modafinil, with clear dose/duration data.

2) Updated and detailed information about the extent of safety information at single and daily doses of 400 mg and greater.

3) Laboratory data for foreign studies

4) Safety update

Pharmacology

[redacted]

Biopharmaceutics

Information about the interconversion of enantiomers was requested.

BEST POSSIBLE COPY

More information about drug interactions with CYP3A and CYP2C19 substrates was requested, and a study to evaluate the interaction of modafinil and clomipramine was requested.

Specific dissolution specifications were requested to be adopted.

In addition, of course, attached to the letter was draft labeling, which provided text in many areas that we requested the sponsor adopt, as well as questions embedded in labeling that the sponsor was to answer.

The sponsor responded to these requests in a submission dated 6/30/98. This submission has been reviewed by Dr. Joel Freiman, clinical reviewer (reviews dated 12/15/98 and 12/16/98), Dr. Aisar Atrakchi and Dr. Glenna Fitzgerald, pharmacology (reviews dated 6/98 and 11/17/98, respectively), Dr. Rae Yuan, Biopharmaceutics (review dated 10/27/98), and Dr. Martha Heimann, chemistry (review dated 7/16/98). Dr. Michael Klein of HFD-170, has performed a number of informal reviews of labeling (some embodied in e-mails) related to abuse potential issues.

In this memo, I will briefly summarize the responses, and offer my recommendations for action on the NDA.

Clinical

As Dr. Freiman notes, based on a detailed examination of Case Report Forms, the sponsor has clarified the number of discrete individuals who have been exposed to at least 1 dose of modafinil. This number is now 2265 (760 domestic, 1505 foreign). Of these, 737 had been exposed for at least 180 days, and 477 for at least 1 year.

We were particularly interested in the experience at daily doses of 400 mg or greater, given the sponsor's desire to include statements in labeling about the safety of this dose. The submission discusses the domestic and foreign data separately. In particular, the sponsor employed a number of assumptions and maneuvers to derive their figures for the foreign data (no such assumptions were needed for the domestic experience).

For example, most of the foreign studies did not expose patients to these doses. Of the 81 foreign studies, these doses were reached in only 26 studies. Of these 26 studies, only 2 had direct information about the dose on any given study day. In the remaining 24 studies, no such direct information was available. Some of these studies employed a fixed dose schedule, some a variable dose schedule.

For the fixed dose studies, the dose the patient was supposed to have received (from the randomization or treatment assignment codes) was determined, and duration of exposure information was obtained from the CRF (although it is unclear if there was any independent way to assess whether or not the patient actually took the dose assigned).

BEST POSSIBLE COPY

For the variable dose studies, only those patients whose ***modal*** dose was at least 400 mg were included in the safety analysis.

Some patients were enrolled into several studies. In these cases, the sponsor presented their total duration of exposure as the total number of days receiving modafinil (even if there had been periods between studies during which they received no drug), and presented the dose received as the average (weighted?) dose they received, when they had been in fixed dose studies.

A total of 680 patients received at least one day of 400 mg/day. Of these, 182 were exposed for between 6 months and 1 year, with an additional 93 exposed for at least 1 year. A total of 128 patients were exposed to at least one day of dosing greater than 400 mg/day, with only 9 of these exposed for greater than 2 weeks. Most of this total dosing was given as a single daily dose (681 of the total 808 patients). Nearly all of the exposure at daily doses of at least 400 mg for more than 90 days was derived in the domestic extensions to controlled trials 301 and 302.

Information on deaths, discontinuations, and serious adverse events are reported from all sources of data as of January 31, 1998.

DEATHS

One death, a 38 year old man who died in a snowmobile accident who had been receiving 400 mg/day, was reported in a US extension study. A second death, a suicide in a [redacted] sponsored study, is discussed below.

DISCONTINUATIONS

Adverse events not previously reported to have resulted in discontinuations included anemia, endometrial CA, leukopenia with elevated liver enzymes, mood change, pruritis, somnolence, goiter, and CHF (and cardiomegaly) in one patient each in the extensions to studies 301 and 302.

In addition, there were 3 unwanted pregnancies in one patient using oral contraceptives, one patient using barrier methods, and one patient using both.

was A 39 year old man who received modafinil in the open extension for about 1 year developed leukopenia and elevated LFTs. On day 290 of treatment, he was noted to have an ALT of 214, AST of 124, GGT of 100, and WBC of 8.3,with 49% lymphs. At discontinuation of drug on day 388 of treatment, his AST was 146, ALT was 305, his GGT was 85, and his WBC was 9.4,with 61% lymphs. Alk Phos was normal throughout, and we have no information on his bilirubin, and no follow-up information.

A total of 43 subjects not previously reported to the NDA in all foreign studies (including Cephalon sponsored named-patient studies, [redacted] sponsored studies, etc.) are now reported to have discontinued due to adverse events. Those ADRs that are of interest in this category include suicide, acute delirium, and visual disturbance. The suicide