

SECTION 8.10**SUMMARY OF POTENTIALLY IMPORTANT ADVERSE EVENTS CONSIDERED
RELATED TO STUDY DRUG:**

Modafinil appears to have a relatively benign safety profile. Although there were occasional cases of clinically significant tachycardia and hypertension clearly related to study drug, in the placebo controlled trials the frequency of these events was similar in the modafinil and placebo treatment groups and most of the clinically significant events occurred at doses higher than the upper limit recommended by the sponsor in their proposed labeling. There was one case of psychosis undoubtedly related to study drug; but there was no evidence of an increased frequency of this AE in modafinil treated subjects at even the highest doses.

Elevated GGT levels did appear to occur with increased frequency in the modafinil treated subjects compared to the placebo treated subjects, in a dose dependent manner. However, none of the elevations were markedly high, a number of the subjects had elevation at screening or baseline, some had other causes likely to explain the elevation (medical history, current medical problem, and/or concomitant medications), and a number of subjects showed decreasing values when they remained on drug. In addition, elevation of GGT in the absence of other liver enzyme elevations and/or elevation of bilirubin may well be due to liver induction, a documented effect of modafinil.

One other issue related to safety should be addressed at this point. In a single small pharmacokinetic study in the elderly, MOD-020, the C_{max} , measured after a single dose of 300 mg of modafinil, was almost twice as high as the C_{max} measured after the same dose in healthy young subjects in Study MOD-018. There did appear to be a high incidence of AE's in the nervous system early in the course of MOD-020, but the patient population in this small, open label trial consisted of hospitalized, elderly subjects with "behavioral problems", making attribution difficult at best. The sponsor has included an upward dose titration for all patients in the recommended dosing schedule, noting in particular the need for that regimen in the elderly. The regimen should provide an adequate margin of safety in the elderly population.

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SECTION 9.0 CONCLUSIONS

In the opinion of this reviewer, the sponsor has demonstrated the efficacy of modafinil in the treatment of excessive daytime sleepiness in patients with narcolepsy.

Based on review of the data submitted, modafinil appears to be reasonably safe when used as recommended.

SECTION 10.0 RECOMMENDATIONS

In the opinion of this reviewer, NDA 20-717 is approvable from a clinical standpoint.

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/S/ [Redacted]

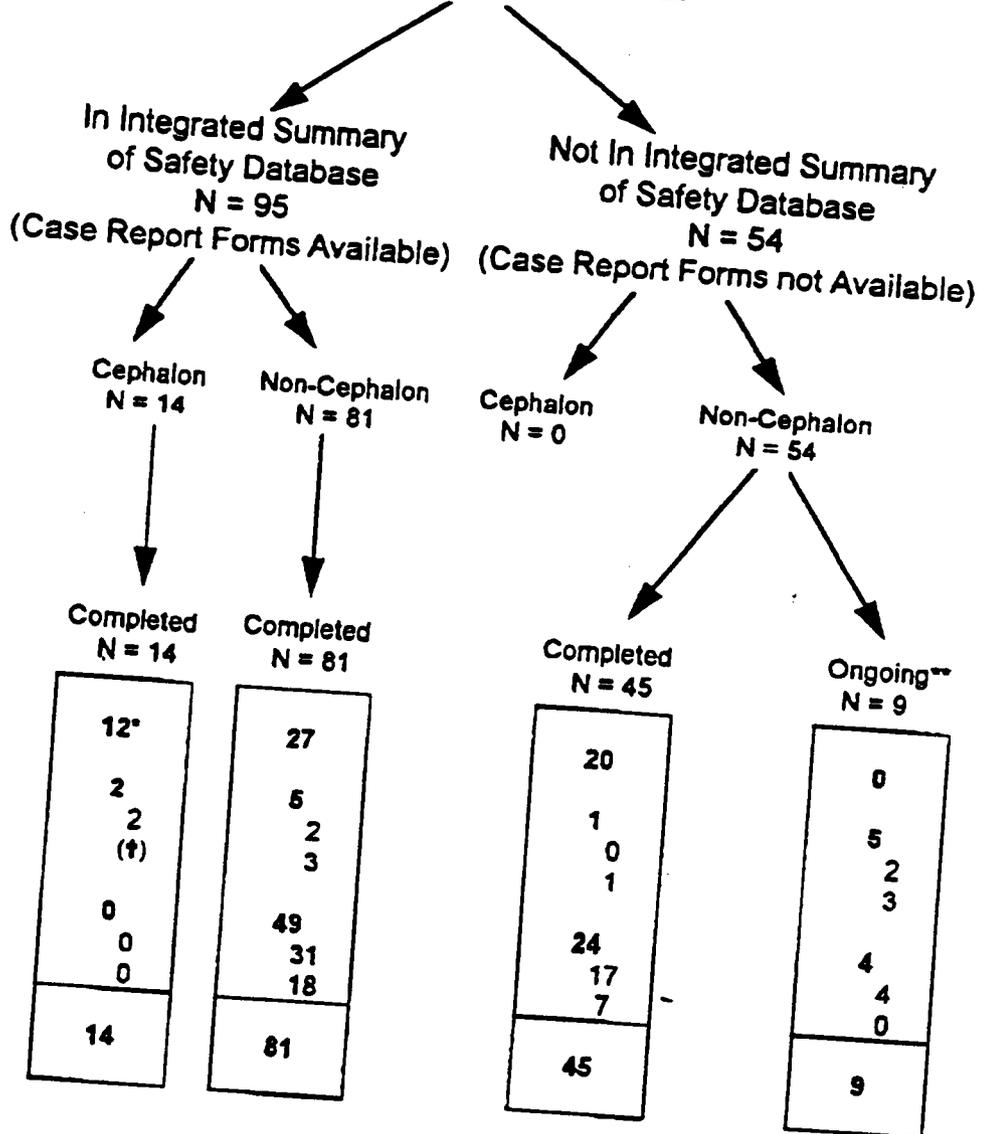
Bob A. Rappaport, M.D.
Division of Neuropharmacologic Drug Products
September 30, 1997

- cc: NDA 20-717
- HFD-120 File
- HFD-120
- Leber
- Katz
- Rappaport
- Malandrucco

APPENDIX I

FIGURE 1

149 Studies Overall



Clinical Pharmacology
Narcolepsy
 Controlled
 Uncontrolled
Non-Narcolepsy
 Controlled
 Uncontrolled
Total

	Completed N = 14	Completed N = 81	Completed N = 45	Ongoing** N = 9
	12*	27	20	0
	2	5	1	5
	2 (†)	2 3	0 1	2 3
	0	49	24	4
	0	31	17	4
	0	18	7	0
	14	81	45	9

* Includes completed portion of abuse liability study (201) and clinical pharmacology component of controlled narcolepsy studies (301 and 302).

† Open-label extensions of controlled narcolepsy studies (301 and 302) through June 15, 1996 cut-off date.

** Ongoing at time of NDA filing.

Table 8.A.1.2-1. Index--Master Table: Cephalon-Sponsored Studies (IND 42,873)

Clinical Pharmacology		Pharmacodynamics		Controlled		Uncontrolled		Other	
Pharmacokinetic	Pharmacodynamic	Controlled	Uncontrolled	Controlled	Uncontrolled	Controlled	Uncontrolled	Controlled	Uncontrolled
1 Single-dose C1538a/103/PK/US (gender/age)	Drug abuse potential (dose-range/gender) 10 C1538a/201/AB/US	13 Adequate and well-controlled C1538a/301/NA/US	13 Open-label continuation/extension (C1538a/301/NA/US)**	Not	Not	Not	Not	Not	Not
2 C1538a/111/PK/US	10 C1538a/201/AB/US	14 C1538a/302/NA/US	14 (C1538a/302/NA/US)**	Applicable	Applicable	Applicable	Applicable	Applicable	Applicable
3 Multi-dose CEP-2101	Dose-range/response 11 C1538a/202/NA/US* 12 C1538a/108/NA/UK**								
4 C1538a/102/MT/US									
5 C1538a/106 (gender)									
6 Drug-drug interaction C1538a/107/PK/UK									
7 C1538a/109/PK/UK									
8 Bioequivalence C1538a/105/BE/UK									
9 C1538a/110/BE/UK									
13 (C1538a/301/NA/US)									
14 (C1538a/302/NA/US)									

Note: There are 14 Cephalon-sponsored studies; the 2 adequate and well-controlled studies each have an open-label 40-week continuation and subsequent 48-week extension treatment period. An additional study (1 patient with idiopathic hypersomnia) was conducted under Investigator IND [REDACTED].

* Administrative termination after enrollment of 1 patient

** Ongoing studies

() Secondary categorization of studies

Abbreviations:
 AB = abuse, BE = bioequivalence, NA = narcolepsy, MD = multiple dose, MT = maximum tolerated dose, PK = pharmacokinetic, UK = United Kingdom, US = United States

TABLE 1

Cephalon-Sponsored Studies (14 studies; included in Integrated Summary of Safety Database)
Clinical Pharmacology Studies (12 studies)

CEP-2101	C1538a/108/NA/UK
C1538a/102/MT/US	C1538a/109/PK/UK
C1538a/103/PK/US	C1538a/110/BE/UK
C1538b/105/BE/UK	C1538a/111/PK/US
C1538a/106/MD/US	C1538a/201/AB/US
C1538a/107/PK/UK	C1538a/202/NA/US

Controlled Narcolepsy Studies (2 studies)

C1538a/301/NA/US
C1538a/302/NA/US

Non-Cephalon-Sponsored Studies (81 Studies; included in Integrated Summary of Safety Database)
Clinical Pharmacology Studies (27 studies)

E803	MOD-015
MOD-001	MOD-016
MOD-002	MOD-017
MOD-003	MOD-018
MOD-004	MOD-019
MOD-005	MOD-020
MOD-006	MOD-021
MOD-007	MOD-022
MOD-008	MOD-023
MOD-009	MOD-029
MOD-010	MOD-030
MOD-011	P1424
MOD-012	P1595/PK5
MOD-014	

TABLE 1 (contd.)

**Non-Cephalon-Sponsored Studies Without Case Report Forms (45 studies;
not included in Integrated Summary of Safety database)**

Clinical Pharmacology Studies (20 studies)

DP-96-014 (A)	683/1-8
MOD-006 (PC2)	690/1-9
MOD-013 (807/PC3)	753/1-10
T1	707/1-11
691/1-2	680/1-12
OPEN/1-3	702/8-3 + 708/8-3
690/1-4	703/8-4
OPEN/1-5	740/8-5
689/1-6	T2
694/1-7	T3

Uncontrolled Narcolepsy Studies (1 study)

Retrospective Compassionate Use

Other Controlled Studies (17 studies)

705/5-5	800/6-5
734/5-6	733/5-3
696/5-7	712/5-4
692/5-8	851/7-10
798/5-9	687/7-7
724/5-10	710/7-8
685/6-1	778/7-4
698/6-2	805/8-2
797/6-3	

Other Uncontrolled Studies (7 studies)

OPEN/7-6	OPEN/7-9
OPEN/5-1	OPEN/7-3
OPEN/5-2	OPEN/8-1
OPEN/7-5	

**Ongoing Non-Cephalon-Sponsored Studies Without Case Report Forms
(9 studies; not included in Integrated Summary of Safety database)**

Controlled Narcolepsy Studies (2 studies)

MOD94003

MOD01

Uncontrolled Narcolepsy Studies(3 studies)

MOD02

E1027

E1028

Other Controlled Studies (4 studies)

E1029

E1030

E1032

E1033

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APPENDIX II

TABLE 25.0.0

CRITERIA FOR DETERMINING CLINICALLY SIGNIFICANT LABORATORY VALUES

	SEX	LOWER LIMIT	UPPER LIMIT
HEMATOLOGY (Continued)			
WBC		<= 2.8	> 16.0
URINALYSIS			
BLOOD			>= 3+
GLUCOSE			>= 500 MG/DL
KETONES			>= 3+
PH		< 4.0	> 9.0
PROTEIN			>= 100 MG/DL
RBC			>= 31/HPF
SPECIFIC GRAVITY		< 1.001	> 1.050
WBC			>= 31/HPF

LLN = Lower Limit of Normal Range ULN = Upper Limit of Normal Range

TABLE PAGE 2

TABLE 25.0.0
 CRITERIA FOR DETERMINING CLINICALLY SIGNIFICANT LABORATORY VALUES

CLINICAL CHEMISTRY (Continued)	SEX	LOWER LIMIT	UPPER LIMIT
TOTAL PROTEIN		< 5.5	
URIC ACID	M		>= 10.5
	F		>= 8.5
Hematology			
BASOPHILS			> 5
EOSINOPHILS			> 5
HEMATOCRIT	M	<= 37	
	F	<= 32	
HEMOGLOBIN	M	<= 11.5	
	F	<= 9.5	
LYMPHOCYTES		<= 15	
MONOCYTES			
NEUTROPHILS			>= 15
PLATELET COUNT		<= 15	
RBC	M	<= 75	
	F	<= 3.8	>= 700
		<= 3.2	

LLN = Lower Limit of Normal Range ULN = Upper Limit of Normal Range

TABLE 25.0.0
 CRITERIA FOR DETERMINING CLINICALLY SIGNIFICANT LABORATORY VALUES

CLINICAL CHEMISTRY	SEX	LOWER LIMIT	UPPER LIMIT
ALBUMIN		< 0.5 * LLN	
ALKALINE PHOSPHATASE			
ALT (SGOT)			>= 3 * ULN
AST (SGPT)			>= 3 * ULN
BICARBONATE			>= 3 * ULN
BUN		<= 20	>= 35
CALCIUM			>= 30
CHLORIDE		< 8.4	> 11.5
CHOLESTEROL		< 90	> 115
CREATININE			>= 330
GGT			>= 2.0
GLUCOSE		< 45	>= 3 * ULN
PHOSPHORUS		< 1	> 160
POTASSIUM		< 3	
SODIUM		< 130	
TOTAL BILIRUBIN			> 5.5
			> 150
			>= 2.0

LLN = Lower Limit of Normal Range ULN = Upper Limit of Normal Range

Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: December 16, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Provigil Tablets (modafinil)
NDA 20-717

TO: File NDA 20-717
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the Division Review Team's recommendation that Cephalon's NDA 20-717, which allows for the use of modafinil tablets (100 mg and 200 mg) in the management of narcolepsy, be declared approvable.

Introduction:

Narcolepsy

Narcolepsy is a clinical syndrome characterized by a constellation of signs and symptoms attributable to a disturbance/dysfunction of CNS systems controlling arousal, sleep, and muscle tone. A neuropathologic basis for narcolepsy has not been established (although pontine abnormalities have been reported on MRI) and diagnosis relies largely on a typical clinical history supplemented by the objective test findings of shortened daytime latency to sleep onset, and rem onset sleep on polysomnography. There is evidence that susceptibility to the disorder lies at a genetic locus closely linked to alleles controlling HLA subtype.

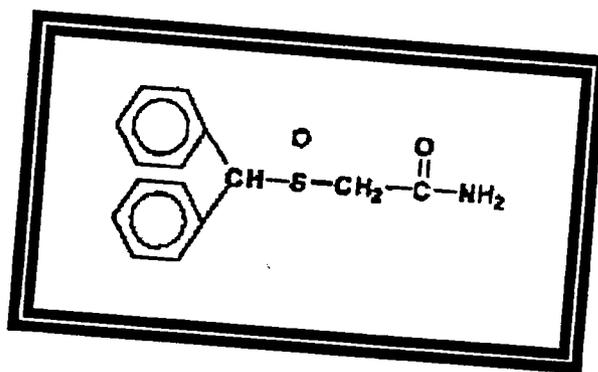
Excessive daytime sleepiness, episodes of "sudden and irresistible" sleep onset in inappropriate settings, drop attacks due to the sudden loss of muscle tone (aka cataplexy), and disturbed nighttime sleep are cardinal clinical features. Sleep associated (awake /sleep interface) disturbances

such as hypnagogic and hypnopompic hallucinations and sleep paralysis are commonly reported epiphenomena. On EEG (polysomnographic EEGs) shortened REM latency (e.g., sleep onset REM) and increased REM density are typical findings.

Current Treatments

Current strategies for the treatment of Narcolepsy are directed at maintaining daytime wakefulness with stimulants (e.g., dextroamphetamine or methylphenidate) AND delaying/reducing sudden onset REM sleep with tricyclic antidepressant drugs (e.g., imipramine). The latter treatment may also reduce the incidence of cataplexy. Gamma-hydroxybutyrate (GHB) is an orphan product currently undergoing evaluation as a treatment for the condition. Also, there are reports of success treating narcolepsy with a number of currently marketed products including selegiline and carbamazepine.

The new drug substance



Possible mechanism of action

Modafinil, 2-[(diphenylmethyl)sulfinyl]acetamide, has been found in both animal and human experiments to promote wakefulness/vigilance. The mechanism through which modafinil operates to produce its clinically useful effects is unknown. A number of indirect modes of action have been postulated. The ip administration of modafinil to rats, for example, causes a decrement in GABA release (ordinarily, an inhibitory neurotransmitter) in CNS regions considered important to arousal and

wakefulness; the decrement in GABA is associated with increases in the local release of both dopamine and glutamate. It has been suggested that an increase in the concentration of either of the latter neurotransmitters in these regions may cause increased arousal/wakefulness. From the sponsor's perspective, the fact that modafinil and amphetamine exhibit different profiles of pharmacologic effects is of potential importance to the former's commercial promotion; it is not so clear whether these differences predict any clinical advantage, however.

Administrative Review Issues

Modafinil has orphan drug status for its use in the management of narcolepsy. The PDUFA date for the application is 12/30/97. Modafinil is the subject of a pending FDA Recommendation that it be placed in Schedule IV under the CSA.

The review documents upon which I relied primarily for my assessment and recommendation are enumerated in the table that follows immediately below.

Documents Considered	Author	date
Team Leader memorandum	Russell Katz M.D.	12/4/97
Supervisory Pharmacology Memorandum	Glenna Fitzgerald, Ph.D.	11/7/97
Clinical Review	Robert Rappaport, M.D.	9/30/97
Statistical Review	David Hoberman, Ph..D.	10/31/97
Pharm Tox Review	Aisar Atrkchi, Ph.D.	3/31/97
CAC Assessment	Joseph DeGeorge, Ph.D.	3/24/97
Full CAC Draft	Wendelyn Schmidt	10/31/97
Biopharm	Rae Yuan, Ph.D.	11/19/97
CMC	Martha Heiman, Ph.D.	12/2/97
Draft CSA Scheduling Recommendation	Michael Klein, Ph.D.	12/1/97

Effectiveness in Use

The review team has identified two adequate and well controlled clinical investigations that provide, within the meaning of the Act, substantial evidence that modafinil is effective in use in decreasing daytime sleepiness in patients with narcolepsy. Modafinil has not been shown to have an effect on cataplexy.

Study Design

The two studies relied upon were conducted in the US; they are identified as **Study 301** and **Study 302**.

Each was a 9 week long, DB, comparison of placebo with 200 and 400 mg daily doses (give qd) of modafinil in narcoleptic patients. The primary outcome measures, the Maintenance of Wakefulness Test¹ (MWT) and Clinical Global Impression of change (CGI-C) were examined at weeks 3, 6 and 9. A MWT for every subject was also obtained at baseline. The MWT score for a subject reflects the mean of 4 administrations of the test to the subject at each visit.

The primary statistical analysis for the MWT was an analysis of covariance employing terms for study site and baseline MWT.

CGI-I was evaluated with a Cochran-Mantel Haenszel (CMH) with strata for baseline severity as determined by the Clinical Global Impression of Severity Score and Site.

No imbalance in groups was found at baseline in either study and, although there were minor differences in the drop-out rates among treatments, the extent of differential attrition was at no point considered an important factor in the interpretation of either trial. The actual retention of subjects by time and by treatment is provided in Table 1 taken from the appendix to Dr. Hoberman's review that follows below.

¹ elapsed time to sleep for an individual in a semi-recumbent position in a dark room who has been instructed to attempt to "stay awake."

Patient Disposition by Visit
Study C1538a/301/NA/US and Study C1538a/302/NA/US (Efficacy-Evaluable)

Study	Treatment Group	No. Patients Randomized	Baseline	Week 3	Week 6	Week 9	Endpoint
301	Placebo	94	92	92	89	87	92
	200 mg/d	95	95	95	94	94	95
	400 mg/d	95	86	85	82	82	86
302	Placebo	93	88	87	87	84	86
	200 mg/d	90	83	83	78	80	83
	400 mg/d	90	86	86	83	84	86
301/302 Combined	Placebo	187	180	179	176	171	180
	200 mg/d	186	178	178	172	174	178
	400 mg/d	185	172	171	165	166	172

Source: Table Following Trial 1,1.
Abbreviations:
mg/d = milligram per day modafinil

Table 1 Retention by Time, From Dr. Hoberman's review.

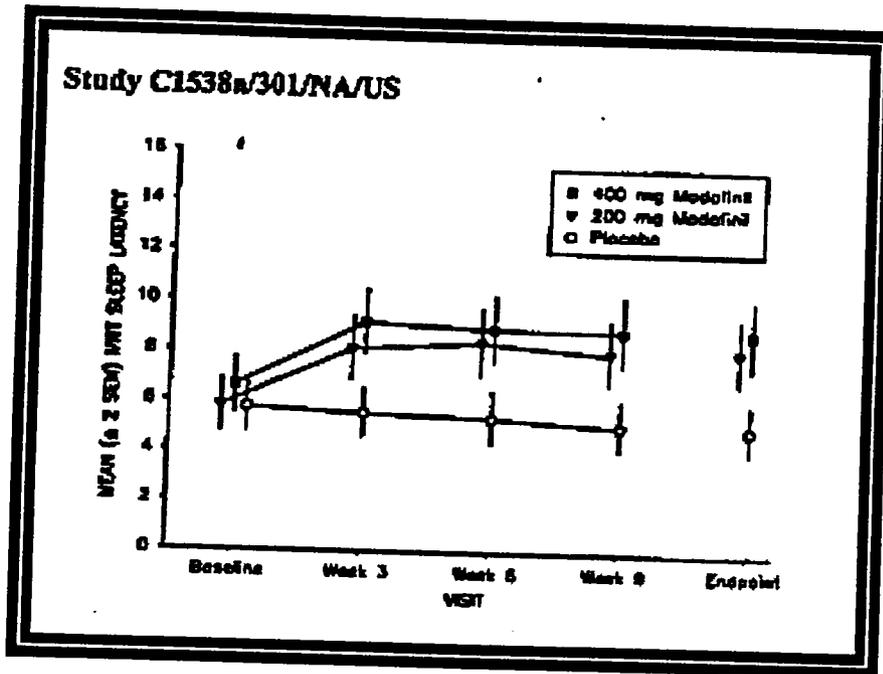
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The following table summarizes the MWT outcomes for Study 301 and 302

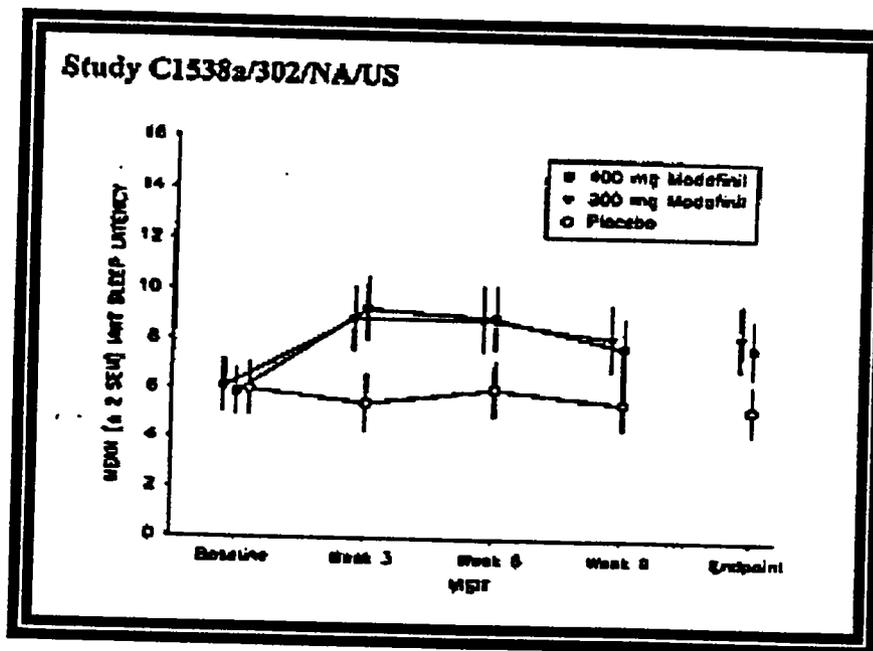
Study	Dose	#	MWT baseline	change in MWT Positive # is improvement	Statistical significance
301	pbo	92	5.8	-0.7	----
301	200	95	5.8	2.3	yes
301	400	86	6.6	2.3	yes
302	pbo	88	6.0	-0.7	----
302	200	83	6.1	2.2	yes
302	400	86	5.9	2.0	yes

The same results are provided in graphical display below. These are also taken from the appendix to Dr. Hoberman's review. (his figure 1)

**STUDY
301**



**STUDY
302**



The CGI-C results provide further support for a beneficial effect of modafinil.

Summary of CGI-C -- Endpoint* Values (Number [%] in Each Category)
Study C1538a/301/NA/US and Study C1538a/302/NA/US [Efficacy-Evaluable]

Study	Response Category	Treatment Group		
		Placebo - N(%)	250 mg/d - N(%)	400 mg/d - N(%)
301	Total Number of Subjects	92	95	86
	Very much improved	4 (4)	7 (7)	5 (9)
	Much improved	2 (9)	25 (26)	35 (41)
	Minimally improved	22 (24)	29 (31)	19 (22)
	No change	43 (47)	27 (28)	20 (23)
	Minimally worse	11 (12)	5 (5)	3 (3)
	Much worse	3 (3)	2 (2)	1 (1)
	Very much worse	1 (1)	0	0
302	Total Number of Subjects	88	85	86
	Very much improved	0	7 (8)	5 (6)
	Much improved	12 (14)	21 (25)	24 (28)
	Minimally improved	21 (24)	20 (24)	23 (27)
	No change	42 (48)	27 (32)	26 (30)
	Minimally worse	9 (10)	7 (8)	5 (6)
	Much worse	4 (5)	1 (1)	3 (3)
	Very much worse	0	0	0
301/302 Combined	Total Number of Subjects	180	178	172
	Very much improved	4 (2)	14 (8)	13 (8)
	Much improved	20 (11)	46 (26)	59 (34)
	Minimally improved	43 (24)	49 (28)	42 (24)
	No change	85 (47)	54 (30)	46 (27)
	Minimally worse	20 (11)	12 (7)	8 (5)
	Much worse	7 (4)	3 (2)	4 (2)
	Very much worse	1 (1)	0	0

Source: Table following Text 11.0.

The validity of a clinician's global assessment of a patient's state of well being in a condition like narcolepsy where that state is largely, if not entirely, known to the clinician only by the patient's self-report is arguable. This is not a challenge to the fact that the patients randomized

to treatment with modafinil preferred their state on active drug to the one prior to randomization. The question raised is whether this preference reflects a true improvement in sleepiness and/or performance. In regard to the latter, I am aware of a report² that sleep deprived individuals given modafinil, compared to those given placebo or dextroamphetamine, were generally less competent at evaluating their extent of actual impairment. Specifically, the abstract² of the study cited reports that, "modafinil had a disruptive effect on self-monitoring, inducing a reliable 'overconfidence' effect (i.e. an overestimation of actual cognitive performance), which was particularly marked 2-4 h post-dose. "

In any event, uncertainties about the basis of global rating assessments offered by clinicians is hardly unexpected, let alone unique. In any event, the MWT, although it seems impossible to know how meaningfully its scores "map" to clinically important facets of wakefulness is an accepted measure used widely in the sleep field. Accordingly, my uncertainties about the global notwithstanding, I am persuaded that it is both reasonable and responsible to conclude that evidence from more than one adequate and well controlled clinical experiment documents that modafinil has a beneficial effect on daytime sleepiness in patients with narcolepsy.

The data also indicate that for the typical individual, a dose of 400 mg a day does NOT provide a greater benefit than a dose of 200 mg a day.

Safety for Use.

Preclinical

The sponsor has yet to provide reports of satisfactory results of all preclinical tests that the agency would ordinarily require be submitted to

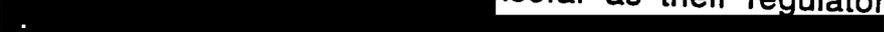
² Baranski JV, Pigeau RA , Self-monitoring cognitive performance during sleep deprivation: effects of modafinil, d-amphetamine and placebo. J Sleep Res 1997 Jun;6(2):84-91

support a regulatory conclusion that a drug is safe for use.

Tumorigenicity testing is incomplete

The sponsor has submitted the result of but one adequate in-vivo life-time carcinogenicity study (a rat study that shows no evidence of tumor inducing potential.). A second in-vivo life-time study was conducted in the mouse, but at systemic exposures deemed inadequate by both the Division review team and the CAC. There is no simple fix for this deficiency, however.

First, modafinil induces its own metabolism in the mouse to an extent that cannot be overcome by merely increasing the administered dose. Accordingly, another preclinical tumor assay is required. However, because modafinil is non-genotoxic, alternatives are limited. In fact, according to Dr. Fitzgerald, that the only viable alternative is the TG.AC assay because it is the "only model for non-genotoxic compounds for which there is some at least some experience.³"

Although I accept Dr. Fitzgerald's implicit conclusion that the in vivo life time CA and TG.AC assays are fungible, at least insofar as their regulatory status is concerned, 



Marginal Teratogenicity and Reproductive performance testing

In Dr. Fitzgerald's view, the "reproductive toxicology studies for modafinil border on the being unacceptable..." The rat fertility study and teratogenicity studies in both the rat and rabbit were not done under GLP. Perhaps even more critically, these studies were conducted at sub-

³ page 2, Dr. Fitzgerald's November 7, 1997 Supervisory Overview

optimal doses. Furthermore, final reports of the GLP compliant peri and post-natal study, a study ordinarily required for NDA approval, has yet to be submitted.

These deficiencies notwithstanding, Dr. Fitzgerald concludes that she can recommend an approvable action because 1) the rat teratogenicity study, albeit conducted at inadequate doses, did establish a threshold dose for teratogenic effects (based on body surface area, the threshold teratogenic dose is only 5 fold that recommended for human use) and 2) preliminary reports of the GLP compliant study indicate that modafinil is unlikely to have adverse behavioral effects on newborns.

In sum, although modafinil's teratogenic effects and its effects on reproductive performance have not yet been fully evaluated, Dr. Fitzgerald believes that these limitations in its assessment are not sufficient, in and of themselves, to justify a not approvable action. Accordingly, Dr. Fitzgerald recommends an approvable action with final approval contingent upon the sponsor's agreement to conduct and submit reports in phase IV of 1) a TG.AC assay and 2) GLP compliant teratogenicity and reproductive performance studies. It is also evident that Dr. Fitzgerald expects that product labeling will identify the deficiencies and limitations of the tests conducted to date.

Clinical Safety

A regulatory determination that a drug is 'safe for use' typically reflects a consensual judgment, offered by a team of agency physicians and scientists, that the risks reported in association with the use of a new drug are, taking into account their kind, severity and incidence, reasonably acceptable in light of the benefits likely to accrue from the use of the drug under the conditions recommended in its proposed product labeling

Although NDA approval always implies a warranty that the product that is the subject of that NDA will be 'safe for use,' under the conditions of use proposed in product labeling, the strength (and value) of the warrant is very much affected by the quality and quantity of clinical experience gained with the drug product during its premarketing development.

Although more than 900 individuals with narcolepsy have been exposed to at least one dose of modafinil, only 344 have been exposed in controlled studies at the doses recommended (i.e., more than 175 mg/d to less than 424 mg/day) for more than 30 but less than 90 days. Including non narcoleptic uses and foreign sources, there are a total of 537 individuals who have been exposed to more than 200 mg/day for 6 or more months and 207 who have been exposed for a year or more. These exposures are sufficient to meet current IH guidance for chronic exposure.

Untoward clinical events and laboratory abnormalities arising from this sea of experience are not in the least alarming. Specific reviews of deaths and premature discontinuations provide no basis for concern.

Although this experience is certainly reassuring about modafinil's common risks, the extent of the experience is relatively limited, and, as a consequence, adverse phenomena regularly associated with the use of modafinil at a dose of 200 mg a day (the recommended daily dose) may not yet be identified.

Biopharmacokinetics

Modafinil is a racemic mixture. There is differential metabolism of the enantiomers (the d isomer is catabolized at a rate 3 fold greater than that of the l isomer); as a result, at steady state, the ratio of the 'l' to 'd' isomers is 9 to 1. There are six metabolites; all are said to be inactive, but there is uncertainty as to how and to what extent they have been evaluated. Metabolism is not affected by age, sex or race.

Abuse and Diversion potential

The drug abuse staff has generated a scheduling recommendation proposing modafinil for placement within Schedule IV of the CSA. (Benzodiazepines are members of this class).

Labeling

There are no unique features or issues vis a vis the product's use in narcolepsy that deserve substantive discussion. I have, however, made

some minor changes in the draft version forwarded to my office, deleting statements in the clinical pharmacology section offering comparisons about modafinil and amphetamine that I believe are of arguable clinical significance.

Discussion

This is a reasonably straight forward approvable action.

One concern, however, is that 'hype' about modafinil's capacity to promote arousal and vigilance without the untoward stimulant like effects of amphetamine may promote its use in a number of non-orphan conditions, notably in children with ADHD. If this were to occur, the major use of modafinil might well become an off label use. Also of some concern is modafinil's potential for diversion and misuse, even abuse. Unfortunately, the extent of the risk is not reliably predictable. Concerns about the potential for modafinil's misuse and abuse explain in large part my decision to strike from product labeling all citations of preclinical studies that have compared amphetamine and modafinil. Not only am I uncertain as to the predictive validity of these studies, but I fear their citation may be used to promote modafinil's use as an alternative to amphetamine.

Recommendation

Issue the approvable action letter and attached draft product labeling.

/s/

Paul Leber, M.D.
December 16, 1997

Leber: Provigil@[modafinil tablets] Approvable Memo

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cc: NDA 20-717

HFD-101

Temple

HFD-120

Katz

Rappaprot

Fitzgerald

Atrakchi

Guzewska

Heimann

HFD-710

Hoberman

Salhroot

HFD-860

Baweja

HFD-170

Klein

McCormick

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MEMORANDUM

DATE: December 4, 1997
FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120
TO: File, NDA 20-717
SUBJECT: Supervisory Review of NDA 20-717, for the use of Modafinil in the Treatment of Patients with Narcolepsy

BACKGROUND

NDA 20-717 was submitted by Cephalon, Inc. on 12/30/96, for the use of Modafinil as a treatment for patients with excessive daytime sleepiness associated with narcolepsy. The sponsor was granted orphan status for this indication in 1993. The drug is approved in France, and application for approval was pending in many European countries at the time of the submission of the NDA.

The application contains reports of many studies, a large number of which were not conducted by Cephalon [REDACTED]. Specifically, a total of 149 studies have been performed. Of this total, 14 were sponsored by Cephalon, and are completely reported; of the remaining 135 non-Cephalon sponsored studies, detailed information is available from 81 (of the 54 studies not completely reported, 9 were on-going at the time of the submission of the NDA, and CRFs were not available for the remaining 45 studies).

Of the 95 studies for which complete information is available, there were 4 controlled trials; 2 sponsored by Cephalon, and which are presented as the 2 adequate and well controlled trials supporting effectiveness, and 2 foreign, non-Cephalon sponsored studies, which are considered supportive.

Data from a total of 2305 subjects treated with Modafinil constitute the safety data base.

The effectiveness data have been reviewed by Dr. Bob Rappaport of the Division (review dated 9/30/97) and Dr. David Hoberman of Biometrics (review dated 10/31/97). The safety data has been reviewed by Dr. Rappaport. The application has also been reviewed by Dr. Atrakchi, pharmacologist (review dated 3/31/97), Dr. Heimann, chemist (reviews dated 4/21/97 and 12/2/97), and Dr. Yuan, pharmacokineticist (review dated 11/19/97).

In this memo, I will briefly review the effectiveness and safety data submitted in support of approval, and give my recommendations for action on the NDA.

EFFECTIVENESS

As noted, the sponsor has sponsored, and submitted the results of, 2 controlled trials which they believe provide substantial evidence of effectiveness. These studies were of essentially similar design.

STUDY 301

This was a randomized, double-blind, parallel group, multi-center, 9 week trial comparing the effect of 2 fixed doses of Modafinil and placebo in patients with narcolepsy.

The protocol was amended many times after the study's initiation, but before data were examined. In particular, the statistical plan was changed several times, and the diagnostic criteria for entrance into the trial was changed (made somewhat more liberal) approximately 5 months after the trial was initiated (approximately 1 year before the entire trial was completed). Approximately half of the patients in this study were enrolled prior to this amendment. The description of the protocol given below incorporates the latest changes prior to unblinding and data analysis.

Patients 18-65 years old meeting the criteria for narcolepsy established

by the American Sleep Disorders Association (published in 1990) were eligible for entrance into the study. Specifically, patients had to have met one of the following 2 minimal criteria (from Dr. Rappaport's review, page 17):

A. Recurrent daytime naps or lapses into sleep which occur almost daily for at least 3 months, plus sudden bilateral loss of postural muscle tone associated with intense emotion. Patients meeting this criteria must have a Multiple Sleep Latency Test (MSLT, to be described later) demonstrating a sleep latency of equal to or less than 8 minutes.

B. Complaint of sudden muscle weakness or excessive sleepiness, plus sleep paralysis, hypnagogic hallucinations, automatic behaviors, and disrupted major sleep episodes; plus polysomnography showing either: 1) sleep latency less than 10 minutes, or 2) REM latency less than 20 minutes, and 3) an MSLT demonstrating a sleep latency of equal to or less than 5 minutes, and 4) 2 or more sleep onset REM periods; plus no other medical or psychiatric disorder that could explain the clinical symptoms.

Patients were not permitted to routinely use antiepileptic medication.

Eligible patients were enrolled into a screening period, followed by a baseline visit. At the Baseline visit, the following were completed:

1) **Epworth Sleepiness Scale**-a scale designed to assess sleepiness in 8 different daytime situations. The scale ranges from 0 (normal) to 24 (worst daytime sleepiness).

2) **"Steer Clear" Performance Test (SCPT)** training session and one SCPT-a computerized test that measures the subject's ability to avoid obstacles in a simulated road display. The test measures the number of obstacles hit, time of each hit, etc.

3) **Two polysomnography sessions**; 1 followed by a **Multiple Sleep Latency Test (MSLT)**, and 1 followed by a **Maintenance of Wakefulness Test (MWT)**:

a) **MSLT**-In this test, the patient is instructed to lie quietly and attempt

to fall sleep. Sleep latency is the time to the first 16 seconds of any stage sleep. In addition, alternate criteria for the determination of sleep latency were used; this was referred to as first continued sleep latency. Other sleep parameters are also measured. Four of these tests are performed in each session. Each test is terminated at 20 minutes if no sleep has occurred.

b) **MWT**-In this test, the patient sits semi-recumbent on a reading pillow in bed in a dark room and is asked to remain awake. The sleep latency is measured in 4 separate tests. Each test will be terminated if sleep has not occurred in 20 minutes.

4) **Patient's Daily Sleep Log**-Patients recorded multiple sleep related measures; e.g., total minutes of daytime sleep, number of night time awakenings, number of episodes of cataplexy, hypnagogic hallucinations, etc.

5) **Quality of Life in Narcolepsy (QOLIN) Inventory-A** Cephalon designed instrument to assess the effect of narcolepsy on the patient's functioning. It is divided into 5 components, each with multiple questions, answered either on an ordinal or visual analogue scale.

6) **Clinical Global Impression of Severity (CGI-S)**

After baseline, patients were randomized to receive one of 3 treatments, each given as a single daily dose (4 tablets):

Modafinil 200 mg/day

Modafinil 400 mg/day

Placebo

There were 2 primary outcome measures:

1) The Maintenance of Wakefulness Test (MWT), which made 4 determinations of sleep latency at each visit Baseline, Weeks 3, 6, and 9).

2) Clinical Global Impression of Change (CGI-C) - a 7 point symmetric scale, centered around no change, and ranging from very much improved to

very much worse.

The protocol specified that the primary effectiveness analysis was to be a comparison of the 400 mg Modafinil group to the placebo group for both the sleep latency on the MWT and CGI-C, with each comparison to be two-sided at the 5% level. The population to be included in the analysis was to be all patients who receive study medication who had at least one post-baseline assessment that consisted of both of the primary measures.

The primary analysis was to be of the last assessment for each patient. The primary method of analysis of the sleep latency (MWT) was to be a generalized ANCOVA which was to include treatment group, center, baseline sleep latency, and other covariates chosen to be determined by a stepwise selection procedure. This procedure was designed to identify any covariates that show baseline variability that significantly correlate with sleep latency at endpoint and any covariates that show clinically significant variability at baseline (description taken from Dr. Rappaport's review, page 19).

The primary analysis of the CGI-C was to be a logistic regression model with terms for treatment, center, baseline severity, and other covariates to be selected as described above.

Other aspects of the data collected on the previously described instruments were to be analyzed as secondary outcomes.

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RESULTS

A total of 285 patients were randomized, with 283 receiving treatment. The following chart displays patient flow (adapted from Dr. Rappaport, page 24):

	Modafinil 400	Modafinil 200	Placebo
Patients randomized	95	96	94
Patients treated	95	96	92
Patients in Efficacy Analysis	86	95	92
Completers	81 (85%)	93 (97%)	87 (93%)

Patients were not included in the efficacy analysis, as noted above, because they did not have at least 1 on-treatment assessment consisting of both measures (MWT & CGI-C). Most of the dropouts were in the 400 mg/day group; most of those discontinuing treatment in this group (11/14) did so for adverse events.

Groups were comparable at baseline on demographics and disease parameters. In particular, patients enrolled in this trial were on average 40-44 years old with a mean duration of symptoms of about 21-23 years (with a mean time since diagnosis of 7-10 years).

Groups were also relatively comparable at baseline with regard to prior medication use and disease severity. For example, similar majorities of patients in all three groups were rated as moderately or markedly ill on the CGI-S (80%, 73%, and 81% for the 400 mg/day, 200 mg/day, and placebo groups, respectively).

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Primary Outcomes

Sleep Latency (MWT)

The following table displays the results:

	Baseline	Endpoint	P-value
Placebo (N=92)	5.8	5.1	
M 200 mg/d (N=95)	5.8	8.2	<0.001
M 400 mg/d (N=86)	6.6	8.9	<0.001

The analysis used was a simple ANCOVA with baseline latency as the only covariate (as described in the protocol, but with no additional covariates included).

As can be seen in Dr. Hoberman's Figure 1, these differences were apparent at Week 3 (the first on-treatment visit) and persisted with little change over the duration of the study. Dr. Rappaport's Table 14, page 32 describes the same information, and notes that the p-values for each dose comparison to placebo at each of these timepoints was <0.001.

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CGI-C

There was a marked change in the distribution of change scores, as outlined in the following table:

	Modafinil 400 (N=86)	Modafinil 200 (N=95)	Placebo (N=92)
Very much improved	9%	7%	4%
Much Improved	41%	26%	9%
Minimally Improved	22%	31%	24%
No change	23%	28%	47%
Minimally Worse	3%	5%	12%
Much Worse	1%	2%	3%
Very Much Worse	0%	0%	1%
P-value	<0.001	<0.001	

The model used baseline severity as a covariate with no other covariates used.

Although the documents submitted with the NDA were not explicit regarding the independence of the rater of the CGI, I discussed this in great detail with the sponsor in a phone call on November 19, 1997. They assured me that the rater (usually, but not always, a physician) had no access to any post-baseline data about the patient at the time of the ratings. Further, every effort was made to ensure that the rater remained the same throughout the study.

As can be seen in Dr. Hoberman's Figure 2, these differences were seen by Week 3, and remained essentially unchanged throughout the trial. Also, the proportion of patients who improved at endpoint was significant at $p < 0.001$ for each dose group compared to placebo (72%, 64%, 37%, for Modafinil 400, Modafinil 200, and Placebo, respectively).

Secondary Measures

A number of secondary outcomes were assessed.

MWT

Multiple other parameters derived from data measured during the MWT were used to compare drug and placebo. These included latency to sleep lasting at least 10 seconds (a standard measure), REM sleep latency, total sleep time, and patient's subjective evaluation of sleep latency. The Agency has not performed independent analyses of these outcomes, but according to the sponsor, the results generally mirror those on the primary outcomes, although for some (total sleep time) the differences, though numerically favoring drug in both dose groups compared to placebo, were not statistically significant, and for REM sleep latency, only the comparison for the 400 mg group reached nominal significance.

MSLT

Again, multiple parameters are measured in this test. These include sleep latency (to the first 16 seconds of continuous sleep), REM sleep latency, first continued sleep latency, latency to Stage 2 and 3 sleep, and patient's subjective evaluation of sleep latency. Again, the Agency has not performed independent analyses of these measures. The sponsor reports consistent and significant between treatment differences for both treatment groups on sleep latency, and first continued sleep latency, but no consistent significant drug-placebo differences for REM sleep latency, Stage 2 and 3 sleep latency, or patient's subjective evaluation of sleep latency.

ESS

ESS scores for each Modafinil group were significantly different from placebo ($p < 0.001$) at endpoint, as well as at Weeks 3 and 6.

SCPT

Between treatment differences between each drug and placebo were.

significant at Weeks 3 and 6, but not at endpoint.

Polysomnography

There were no consistent significant differences between either drug group and placebo on any parameters.

Patient Sleep Log

In general, the sponsor reports changes favoring drug on various sleep related measures, but not statistical analyses were presented.

QOLIN

Although the sponsor reports changes in favor of drug, no statistical analyses were reported.

STUDY 302

This study employed a design that was essentially identical to that of Study 301, with the one difference being a 2 week withdrawal phase at the end of the 9 week controlled trial (as in Study 301, the sponsor submitted an amendment to change the diagnostic criteria to those adopted by the American Sleep Disorders Association; unlike Study 301, this amendment was submitted prior to enrollment beginning in Study 302. Therefore, all patients in this study were admitted under the more recent criteria).

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