Table II. Deaths: All studies.

Subject	Dose (mg/d)	Duration of therapy (d)	AEs preceding death	Severity	Relatedness
40 yr F (ALS)	200	Unknown	Aggravation Reaction	Severe	Not related
82 yr F (Depression)	150	1	Heart failure, Pain, Kidney Function Abnormality, Flatulence	Life-threatening	Not related
65 yrs F (major depressive episode)	200	unknown	syncope, dyspnea	Life-threatening	Unknown
68 yrs F (Age assoc. Memory impairment	400	unknown	Asthenia*	Unknown	Unknown
58 yrs M (major depressive episode)	200	8	Aggravation of encephalopathy	NE	Not related**

* Database indicated asthenia at cause of death; actual cause of death was MI.
** Narrative indicated that "advanced cirrhosis of liver could be totally responsible for outcome."

ADVERSE EVENTS FOLLOWING WITHDRAWAL OF THERAPY. Effects of discontinuation from modafinil were assessed in a pivotal efficacy and safety study, wherein patients were taken off drug during a 2-week period before start of an open label extension period. Frequency of new AE's was comparable between subjects discontinued from placebo, 200 mg/day modafinil, and 400 mg/day modafinil. Patients who completed the 9 week double-blind phase, or who terminated for reasons other than noncompliance or a medication related adverse event, then participated in a 2-week double-blind withdrawal phase before entering the open label phase. Patients were randomized to a withdrawal period as follows: 20% in the 400 mg/day group; and 20% in the 200 mg/day group.

The Adverse Event profile for the withdrawal phase was not significantly different for patients who were withdrawn from modafinil treatment compared to those who continued to receive placebo. There was no specific evidence of an amphetamine-type withdrawal syndrome; however since approximately 80% of the subjects were receiving concomitant CNS active medications (including other stimulants), the significance of this data is questionable.

Effects of discontinuation from modafinil were also assessed in Parkinson's disease patients and normal subjects. As seen in the pivotal efficacy and safety studies, no withdrawal syndrome was associated with modafinil. Parkinson's disease patients treated with 200 or 300 mg/d of modafinil for 21 days experienced no withdrawal symptoms during a 7-day observation period. Likewise, normal subjects treated with 200 to 1000 mg of modafinil for 7 days were observed during a withdrawal period of 3 days. The only AE possibly possibly related to withdrawal was occurrence of drowsiness in 7/8 patients who completed dosing in the 1000 mg/day group.

The body system with the greatest number of adverse events was the CNS with 16 likely/possible. Eight of these 16 costart terms were either nervousness/anxiety/agitation. The body system with the next most frequent mention was the gastrointestinal system, with nine likely/possible, four of these nine being dry mouth. The systems in diminishing order of frequency follow: cardiovascular with six events (four of the six being tachycardia); dermatologic with four events (all four being rashes of various sorts); endocrine/metabolic with four events; musculoskeletal with three events; and various miscellaneous events comprising five events (including two cases of increased sweating).

WHO Adverse Reactions database up to July 1997, was reviewed as well. There appeared to be no

discernible pattern of events from this database and causation was difficult to establish. The only "new" events listed that were not in the clinical study database included urinary incontinence, dyskinesia, malaise, hypertension, and tinnitus.

Table III. AEs in Subjects Leading to Discontinuation from Study - By COSTART Terms

BODY SYSTEM Costart Term	Subjects Discontinued Due to Specified AE N (%)	
	CLINICAL STUDIES	
	Modafinil (N=2305)	Placebo (N=1050)
NERVOUS SYSTEM	**723 (31.4)**	**236 (22.5)**
Nervousness	172 (7.5)	45 (4.3)
Insomnia	178 (7.7)	37 (3.5)
Anxiety	116 (5.0)	23 (2.2)
Somnolence	66 (2.9)	51 (4.9)
CNS Stimulation	82 (3.6)	22 (2.1)
Sleep Disorder	63 (2.7)	25 (2.4)
BODY AS A WHOLE	**622 (27.0)**	**221 (21.0)**
Headache	402 (17.4)	113 (10.8)
Asthenia	89 (3.9)	33 (3.1)
Infection	59 (2.6)	32 (3.0)
Abdominal Pain	69 (3.0)	15 (1.4)
DIGESTIVE	**403 (17.5)**	**103 (9.8)**
Nausea	148 (6.4)	23 (2.2)
Anorexia	80 (3.5)	7 (0.67)
Dry Mouth	76 (3.3)	11 (1.0)

ADVERSE EVENTS ASSOCIATED WITH DROPOUTS. The most commonly observed AE's in modafinil-treated subjects (not seen at an equivalent incidence in placebo-treated subjects) were: headache, nausea, diarrhea, dry mouth, anorexia, nervousness, dizziness, rhinitis, and pharyngitis (See Table III, above). The most frequent AEs in modafinil-treated subjects compared to subjects on placebo were headache and nausea. AEs of clinical concern that resulted in discontinuation from study were primarily cardiovascular-related.

ADVERSE EVENTS ASSOCIATED WITH LONG TERM USE. Forty of 478 (8%) subjects discontinued due to AE's in the Phase 3 open label studies compared to 5% in the Phase 3 double blind studies. This small difference is likely due to the significantly longer duration of the open label trials (52 weeks vs. 9 weeks). AE's leading to discontinuation were similar in the double blind and open label studies. Seventeen of the 478 (4%) subjects in the open label studies discontinued because of development of

nervous system AEs: including nervousness (7 subjects), anxiety (4), depression (3) and cataplexy (2 subjects). Other long term studies (1 year or longer) resulted in seven of ten subjects withdrawing or being discontinued due to the following AEs: salivation disorders, restless legs, nausea, anxiety and "internal tension."

In another study, 319 subjects received 50 to 600 mg per day, and readjusted most commonly to a maintenance dose in the 100 to 300 mg/day range. Duration of treatment ranged from one month to ten years. Eighty-one subjects received modafinil for 1 year or longer and 37 subjects received modafinil for at least 3 years. Sixty-seven subjects reported a total of 319 AEs: including irritability, sleep disorders, headaches, and gastric pain. Ten subjects withdrew because of the following AE's: depression, gastric pain, asthenia, dyspnea, nervousness, cutaneous eruption, anorexia and "poor tolerance." There were three serious AEs: myocardial infarction, cranial trauma and abdominal surgery for stenosis.

CLINICAL ABUSE LIABILITY TRIALS. The potential abuse liability of orally administered modafinil using methylphenidate as a reference agent was evaluated in a double-blind, placebo-controlled, 6x 6 Latin square crossover, inpatient study. Each drug evaluation session was separated by two washout days. Doses were chosen on the basis of the results of a dose ranging study. Each subject received two doses of methylphenidate (45 mg and 90 mg), three doses of modafinil (200, 400 and 800 mg), and placebo in a randomized, double-blind manner. The study was conducted in male (n= 24; 30-46 years old) and female (n=12; 30-40 years old) subjects with a history of polysubstance abuse that included cocaine. The treatment sequence for male subjects was different than the sequence for the female subjects. The criteria for evaluation included the Addiction Research Center Inventory (ARCI) subscales, Drug Rating questionnaires, Drug Identification questionnaires, Specific Drug Effect Questionnaire and functional and physiological measurements.

On the ARCI Amphetamine (Stimulant) Subscale in the male group, maximal response for modafinil 800 mg was observed at 1 hour, which was greater than that of modafinil 200 mg, modafinil 400 mg and placebo. On the same Scale, the female group's maximal responses for modafinil 200 mg and 800 mg were greater than that of placebo. On the ARCI Benzedrine (Stimulant) Subscale, the male subjects did not identify modafinil as an stimulant. Methylphenidate 90 mg was identified as an stimulant within 1 hour after dosing. In contrast, the female subjects, identified modafinil 200 mg as an stimulant. The maximal response for modafinil 200 mg was observed at 1.5 hours and it was greater than that of modafinil 400 mg.

On the important ARCI Morphine-Benzedrine (Euphoria) Subscale, in the male group modafinil 200 and modafinil 400 mg produced little difference from placebo. A dose-dependent effect for this measure was apparent for both methylphenidate and modafinil. As it was observed in the Amphetamine Subscale, the peak effect for modafinil 800 mg occurred within 1 hour. The response for modafinil 800 mg fell between that of methylphenidate 45 mg and methylphenidate 90 mg. In the female group, the response for modafinil 800 mg was greater than both methylphenidate doses and modafinil 400 mg.

On the Sedation Subscale of the ARCI (Pentobarbital-Chlorpromazine-Alcohol Group), in males and females the maximal responses for all doses of methylphenidate and modafinil were similar to that of placebo. On the Dysphoria or Hallucinogenic Subscale (Lysergic Acid Diethylamide Group), both modafinil 800 mg and methylphenidate 90 mg produced similar dose-response curves in males. The response for methylphenidate 90 mg was greater than that of modafinil 800 mg. In females, the response for modafinil 800 mg was greater than that of methylphenidate 45 mg. The intensity of the LSD responses increased as the responses on the stimulant subscale decreased.

The Drug Rating Questionnaire is a four-item questionnaire in which the subject indicates "drug liking", "drug disliking" and if "felt the drug's effect" and whether "felt high". To the question "Feel the drug",

in males, both doses of methylphenidate and the 800 mg dose of modafinil were discriminated from placebo and the maximum effect for modafinil 800 mg which was achieved at one hour was intermediate to that of methylphenidate 45 mg and 90 mg. In the female group, the response observed for modafinil 800 mg was greater than that of methylphenidate 45 mg and 90 mg and a dose-dependent effect was observed for modafinil and methylphenidate.

To the question "Like the drug effect", in males, a dose-dependent effect for this measure was apparent for both methylphenidate and modafinil and the response for modafinil 800 mg was similar to that of methylphenidate 90 mg; the maximal response was achieved in one hour. In the female group, the maximum responses for modafinil 200 and 400 mg were slightly higher than those of both doses of methylphenidate. The maximal response for modafinil 800 mg was higher than the response produced by methylphenidate 90 mg and occurred at 2.5 hours.

To the question "Dislike the drug effect", in males, the response obtained for modafinil 800 mg was similar to that of methylphenidate 90 mg and the maximum responses for all modafinil doses were lower than those produced by both methylphenidate doses. In females, the responses for modafinil 400 mg and 800 mg were similar to those of methylphenidate 45 and 90 mg respectively. To the question "Do you feel high", in males, a dose-dependent effect for this measure was apparent for both methylphenidate and modafinil. Both doses of methylphenidate and the 800 mg dose of modafinil produced statistically significant elevations compared to placebo. The response for modafinil 800 mg was intermediate to that of methylphenidate 45 mg and 90 mg and greater than modafinil 200 mg. In females, also a dose-dependent effect for this measure was apparent for both methylphenidate and modafinil and the response for modafinil 800 mg was greater than both methylphenidate doses and modafinil 200 and 400 mg.

In the drug identification questionnaire in males and females, the effects of both methylphenidate and modafinil were predominantly identified as stimulant-like, with positive identifications reported by the majority of subjects for methylphenidate (45 mg and 90 mg) and for modafinil (400 mg and 800 mg).

In drug response questionnaire, male and female subjects reported "body feels different, changed", "nervous" and "stomach turning" following administration of methylphenidate and modafinil compared to placebo. Subjects also reported a "need to talk" following all active doses with the exception of modafinil 200 mg. Fewer male subjects reported feeling "sleepy" or "relaxed" following modafinil dosing compared to placebo and methylphenidate. In females, modafinil 400 mg and 800 mg resulted in a greater number of reports of "full of energy" and modafinil 200 mg had increased reports of "stomach turning" and modafinil 800 mg had increased reports of "afraid". In the same questionnaire, the observer's evaluation differed from the male subjects in that there were more reports of "talking", "nervous" and "anxious" and fewer reports of "nodding" for methylphenidate and modafinil; and fewer reports of "sleepy" and greater responses of "active" occurred for modafinil compared to methylphenidate and placebo. The observer also reported for the female group a greater number of "talking" responses and fewer "sleepy" and "nodding" responses for methylphenidate and modafinil. More "active" responses were observed following administration of modafinil.

Both methylphenidate and modafinil produced dose-dependent reductions in the number of observed and reported hours of sleep relative to placebo in male and female subjects. Also, reduction of appetite was assessed by caloric intake count. In both groups, all doses of methylphenidate and modafinil reduced caloric intake at the noon meal relative to placebo, and methylphenidate 90 mg and modafinil 400 and 800 mg produced statistically significant reductions in combined caloric consumption at the noon and evening meals compared to placebo.

In both groups a dose-dependent increase in supine and standing systolic and diastolic blood pressure; and positive correlation between blood pressure and standing pulse rate was observed for methylphenidate and modafinil.

3. The state of current scientific knowledge regarding the drug or other substance.

CHEMISTRY. Modafinil, registry number CAS-68693-11-8, is 2-[(diphenylmethyl)sulfinyl]-acetamide. It is also known by the code names CRL 40476 and CEP 1538. Its molecular formula is $C_{15}H_{15}NO_2S$; the molecular weight is 273.36. Modafinil (Provigil) is a tablet with 100 mg or 200 mg of active ingredient. The product contains talc. [redacted] modafinil has little structural similarity to any of the known CNS stimulants (e.g. cocaine, amphetamine, methamphetamine or pemoline).

Modafinil is white to off-white crystalline powder that is practically insoluble in water (10 mg/100 mL) and cyclohexane, slightly soluble in ethanol (1 mg/mL) and soluble in methanol (10 mg/mL). It is sparingly to slightly soluble in methanol and acetone. [redacted]

[redacted]

PHARMACOKINETICS (HUMAN). Modafinil is well-absorbed after oral administration. Peak plasma concentration occurs at 1-4 hours. Elimination half-life was 9 to 14 hours after a single oral dose of 200 or 400 mg. Both modafinil and modafinil acid exhibited linear pharmacokinetics over a dose range of 50-499 mg. Oral bioavailability of a 200 mg tablet relative to a micronized aqueous suspension was close to 100%. Apparent volume of distribution of modafinil was larger than the volume of total body water (0.6 L/kg). Females (35%) appeared to excrete less modafinil acid in urine than males (51%). Clearance of modafinil in males decreased slightly (approximately 10-20%) as the age increased. Stereospecific pharmacokinetics of enantiomers have been demonstrated. The *dextro*-isomer was eliminated faster (100-140 mL/min) than the *levo*-isomer (35-50 mL/min).

Modafinil was extensively metabolized after oral dosing by deamination, oxidation, and aromatic ring hydroxylation. Total oral clearance of modafinil after a single dose was approximately 60 mL/min. Less than 10% of the dose was excreted in urine as parent drug. Modafinil acid accounted for 50-60% of the dose in males and 30-40% in females. Urinary excretion of modafinil sulfone was negligible. Renal clearance of modafinil accounts for 5-6% of plasma clearance, indicating that modafinil is primarily eliminated by liver metabolism. After a single dose of side-chain labeled ^{14}C-modafinil, 79.6 ± 5.9% and 1.0 ± 0.3% of the dose was recovered in urine and feces, respectively, over an eleven day period.

After multiple once daily 200, 400, and 600 mg dosing, apparent steady-state plasma levels were reached after 2-4 days of dosing. Elimination half-life after the last dose of multiple dose regimen was 13-18 hours. Modafinil was moderately bound to plasma proteins (61-65%), primarily albumin. Food delayed absorption of modafinil (Tmax: 3.21 vs. 2.05 hours). However, AUC and elimination half-lives did not differ between fasted and fed conditions. In patients with renal impairment, elimination of modafinil acid was reduced after a single dose of 200 mg. Only 25% of the modafinil dose was excreted in urine as modafinil acid in patients with renal insufficiency. Forty-five percent of the modafinil dose was excreted as modafinil acid in the urine of healthy subjects.

In a multiple dose study (200 mg/day) for 8 days in patients with liver cirrhosis, patients exhibited high modafinil AUC and extended half-life, suggesting that the major elimination route of modafinil was liver. In a single-dose pharmacokinetics interaction study with methylphenidate and modafinil, no clinically important alterations in the pharmacokinetics profile of either drug was noted. A delay in oral absorption of modafinil was observed (Tmax of 2.9 vs. 1.9 hours).

An open label, multiple dose, study in elderly male and female volunteers followed administration of 300 mg/day modafinil for 7 days. Plasma levels were determined on days 1 and 7. Maximum plasma concentrations after the first dose were much higher in healthy young volunteers. Plasma levels of modafinil obtained from day 7 were higher than those of day 1. This implied occurrence of accumulation after 7 days of daily dosing of 300 mg modafinil in elderly subjects.

The pharmacokinetics portions of the pivotal Phase III efficacy trials were designed to evaluate the steady state plasma trough levels of modafinil and its two metabolites, modafinil acid and modafinil sulfone. After daily dosing of 200 mg modafinil, plasma trough levels of modafinil and the two metabolites reached steady state by Week 3 and remained unchanged through Week 9. After daily doses of 400 mg modafinil, the plasma trough levels of modafinil at Week 9 were significantly lower

(approximately 20%) than those of Week 3. The two metabolites did not show this difference. Also, the plasma trough levels of modafinil sulfone were negatively correlated with age, suggesting metabolism of modafinil to modafinil sulfone might be slower in older patients. Also, plasma levels of modafinil sulfone from female patients in the 400 mg group were higher than those of male patients at Weeks 3 and 6.

4. Its history and current pattern of abuse.

Marketing authorization in France was granted in 1992, although the product was not commercially available there until 1994. Initially, modafinil could only be obtained through restricted prescription, that is, it was only obtained from a public neurologist and dispensing hospital pharmacies. In November of 1995, the prescribing requirements were relaxed by the French Health Ministry in accordance with the schedule for exceptional drugs of restricted prescription. This requires that the prescription be restricted to specialists and physicians working in departments of neurology and public or private sleep centers, with dispensing by retail pharmacists. General practitioners may renew prescriptions, provided that the specialist carries out a clinical assessment every year, and that a specialized evaluation (polysomnography followed by a Multiple Sleep Latency Test) be performed every 5 years. [redacted] filed a Multistate Application in October 1994 to: Belgium, Denmark, Greece, Ireland, Italy, Netherlands, Portugal, Spain and the U.K. Objections were raised by the member states and in October 1996, responses were submitted to the CPMP for evaluation. At the time of submission of the NDA, approval was pending in 13/14 European countries, France being the only European state where the drug has been approved.

A [redacted] licensee submitted its [redacted] marketing application in May 1993. The application was rejected due to a lack of sufficient data to assess efficacy. It was supplemented and resubmitted in August 1996, with approval pending. According to Cephalon, since the 1994 date of commercial availability of modafinil in [redacted] has not issued any warning letters to the prescribing physicians.

Although modafinil's duration of action, onset and offset of its subjective and other CNS related effects are virtually instantaneous. This implies existence of a close association between behavioral administration and onset of effect leading to reinforcement and heightened abuse potential. Comparable effects of the reference stimulants appear to develop more slowly, although the duration of effects is much longer.

As a drug of abuse, methylphenidate has a history of abuse. When abused, the most common route of administration for amphetamine derivatives is intravenous, although it can be smoked, taken orally, transmucosally or intranasally. No studies examining alternative routes of modafinil administration (s.c., intradermally, im, po, or transdermally) have been completed in humans. Animal studies indicate that modafinil is poorly absorbed by the oral and dermal routes, but was well absorbed following intratracheal inhalation or ocular application.

Modafinil and its N-hydroxy analog, adrafinil, can be purchased without any restriction through the Internet. Both drugs are advertized as "smart drugs" which promote vigilance and alertness. Modafinil is approximately ten-fold more expensive than adrafinil: Modafinil, Modiodal, 100 mg, $640 per 120 tablets; Adrafinil, Olmifon, 300 mg, $22 per 40 tablets). Different routes of synthesis are described in the literature. Adrafanil is also commercially available in France and is indicated in the treatment of sleeping and attention deficit disorders. [redacted]

5. The scope, duration, and significance of abuse.

There are no reports of abuse of modafinil (See 4. History and current pattern of abuse). The product has not been widely marketed throughout world. Currently, it is only marketed in France. Abuse of modafinil would be for similar reasons that other currently available CNS stimulants, such as amphetamine, methamphetamine, and dextroamphetamine are abused. Were modafinil marketed as a noncontrolled CNS active stimulant, the individual who abuses such drugs would likely prefer to use PROVIGIL®, for its noncontrolled status, rather than amphetamine, methamphetamine or methylphenidate, which are controlled under the CSA, and are therefore more difficult to acquire by individuals not registered with the Drug Enforcement Administration.

One currently accepted criterion for predicting abuse liability of a new drug relies upon measurements of measuring subjective and objective responses of "drug-aware" subjects to both new and reference drugs. Human drug abuse liability testing indicate that modafinil has an abuse potential that is greater than placebo and equal to or greater than methylphenidate in its peak effects. This property appears to be especially pronounced in female subjects. The abuse liability of oral modafinil was assessed relative to methylphenidate in CNS psychostimulant-experienced individuals. Both drugs are CNS stimulants with effects mediated primarily through dopamine reuptake inhibition sites. Modafinil, however, is less potent on a milligram to milligram basis than methylphenidate or amphetamine or methamphetamine, and is primarily active by the oral route.

Both modafinil and methylphenidate have typical CNS psychostimulant effects and as such each has the potential to be abused. The principal difference between the two drugs is that modafinil is not water very soluble and therefore is not likely to be abused by intravenous injection as the amphetamines and methylphenidate are abused at times. Modafinil also decomposes upon heating; therefore, modafinil is not likely to be abused by the smoking route. Similarities between modafinil and methylphenidate were found both for its physiologic effects and for subjective reports such as liking and other pleasant effects related to abuse liability. Modafinil was as well tolerated as methylphenidate in psychostimulant experienced subjects.

At greater than therapeutic dose levels, modafinil has been recognized as amphetamine-like in behavioral studies [Addiction Research Center Inventory (ARCI)] in post-addict volunteers. In the other critical subscales of the ARCI, modafinil produced high scores on euphoria, stimulant, and hallucinogenic subscales; modafinil was compared in these double blind studies against placebo and methylphenidate as a positive control.

6. What, if any, risk there is to the public health.

Individuals may likely become dependent on modafinil, and suffer adverse consequences of modafinil overdosage if abused. Easy availability and ease of *ad lib.* administration by the oral route may be expected to contribute to risk of overdosage.

PROVIGIL® presents the same risks to the public health as those resulting from administration of other orally active CNS stimulants which are readily available in hospitals, clinics, and at the retail level. Past outbreaks of diversion and abuse of amphetamine and its analogues have resulted in public health problems. Nonmedical and improper administration may more likely lead to overdosage and production of dependence and tolerance as is seen with other CNS stimulants.

7. Its psychic or physiological dependence liability.

A comparative evaluation of the dependence potentials of modafinil versus cocaine in primates is inferred from self-administration of drug following administration of cocaine as training drug. The self-administration paradigm is widely used to determine whether or not a drug can control behavior, that

is, function as a positive reinforcer, and is used to assess the abuse potential of the substance. Self-administration studies using nonhuman primates and rats have been shown to be a valid and reliable predictor of the potential of a substance to result in drug dependence (i.e., addiction). There is a strong concordance between the types of drugs that serve as reinforcers in animals and the many illicit drugs associated with problems of dependence, addiction, and abuse in man (Johanson and Balster, 1978; Griffiths *et al.*, 1980; Woolverton and Nader, 1990). The reinforcing effects of modafinil were evaluated in rhesus monkeys experienced in self-administration of intravenous cocaine under a fixed ratio 10 schedule of reinforcement. Modafinil maintained FR 10 responding at rates that exceeded saline self-administration at one or more doses. Modafinil maintained FR 10 responding in all monkeys tested.

The results from the study clearly demonstrated that modafinil can function as a positive reinforcer in monkeys trained to self-administer cocaine as their baseline drug. These results suggest that modafinil has the potential to be a drug of abuse in individuals with a history of stimulant abuse. However, one can not rule out the possibility that modafinil may become a drug of abuse in individuals who have no history of substance abuse.

Discriminative stimulus properties of modafinil were analyzed in rats trained to discriminate cocaine (10.0 mg/kg, i.p.) from vehicle. Modafinil (250 mg/kg) produced cocaine-appropriate responding in four out of six rats. Modafinil (250 mg/kg) also reduced response rates.

8. Whether the substance is an immediate precursor of a substance already controlled under this title.

Modafinil is not readily convertible to other controlled substances.

RECOMMENDATION

After consideration of the eight factors determinative of control of a substance [21 U.S.C. 811(c)], which are referred to above, the FDA recommends that because of its abuse potential which is comparable with substances which are controlled in Schedule IV of the Controlled Substances Act, modafinil (PROVIGIL®) should be controlled similarly in Schedule IV. The necessary criteria for placing a substance into Schedule IV of the CSA, as set forth in 21 U.S.C. 812(b)(2), as follows:

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.

Modafinil (PROVIGIL®) has a potential for abuse equal to or greater than those CNS stimulants that are listed in Schedule IV and available on the retail market, but with some properties which limit its abuse potential. Modafinil elicits many of the same pharmacological responses and adverse reactions as those of the classical psychostimulants. Its short duration of action and rapid onset further enhance the likelihood that modafinil would be abused. The physical properties of modafinil are likely to limit its actual abuse. Although modafinil was self-administered by primates when substituted for training drug cocaine, it was only partially discriminated as amphetamine-like by rats in drug discrimination studies.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

Upon FDA approval of its currently pending new drug application, PROVIGIL® (modafinil) will be able to be marketed in the United States for treatment of narcolepsy.

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

The dependence capacity of modafinil can be inferred from preclinical data and an overall clinical pharmacology profile which relate its drug discriminative properties, reinforcing efficacy, and adverse events to other CNS stimulants. From preclinical studies, the dependence capacity data of modafinil is shown to be equivalent to that of other CNS stimulants (including cocaine, methylphenidate, amphetamine and methamphetamine). Modafinil is likely to be used to suppress a withdrawal syndrome upon withdrawal of other stimulants. Physical dependence, tolerance production and a withdrawal syndrome may result after abrupt discontinuation of modafinil following excessive use. The indication of a possible mild withdrawal syndrome from clinical trials, typified by tiredness, occurred upon discontinuing usage of modafinil.

PUBLISHED LITERATURE

1. Abel-Coindoz, C.; Vezin, H.; Daveloose, D.; Roussel, B.; Viret, J.; "Study by EPR of structural modifications on liposomes induced by metabolites of modafinil," Ann. Pharm. Fr., 51(4): 197-204, 1993.

2. Akaoka, H.; Roussel, B.; Lin, J. S.; Chouvet, G.; Jouvet, M.; "Effect of modafinil and amphetamine on the rat catecholaminergic neuron activity," Neurosci. Lett., 123(1): 20-2, 1991.

3. Besset, A.; Chetrit, M.; Carlander, B.; Billiard, M., "Use of modafinil in the treatment of narcolepsy: a long term follow-up study," Neurophysiol. Clin., 26(1): 60-6, 1996.

4. Bettendorff, L., Sallanon-Moulin, M.; Touret, M.; Wins, P.; Margineanu, I.; Schoffeniels, E., "paradoxical sleep deprivation increases the content of glutamate and glutamine in rat cerebral cortex," Sleep, 19(1): 65-71, 1996.

5. Billiard, M., "Narcolepsy," Rev-Prat., 46(20): 2428-34, 1996.

6. Billiard, M.; Besset, A.; Montplaisir, J.; Laffont, F.; Goldenberg, F.; Weill, J.S.; Lubin, S.; "Modafinil: a double-blind multicentric study," Sleep, 17 (8 Suppl): S107-12, 1994.

7. Bourdon, L.; Jacobs, I.; Bateman, W.A.; Vallerand, A. L.; "Effect of modafinil on heat production and regulation of body temperatures in cold-exposed humans," Aviat. Space Environ. Med., 65(11): 999-1004, 1994.

8. Carceller, E.; Merlos, M.; Giral, M.; Almansa, C.; Bartroli, J. I.; Garcia-Rafanell, J.; Forn, J., "Synthesis and structure-activity relationships of 1-acyl-4-[(2-methyl-3-pyridyl) cyanomethyl]piperazines as PAF antagonists," J. Med. Chem., 36:2984-97, 1993.

9. De Sereville, J. E.; Boer, C.; Rambert, F. A.; Duteil, J.; "Lack of pre-synaptic dopaminergic involvement in modafinil activity in anaesthetized mice: in vivo voltammetry studies," Neuropharmacology, 33(6): 755-61, 1994.

10. Disdier, P.; Genton, P.; Milandre, C.; Bernard, P.M.; Millet, Y.; "Fibrositis syndrome and narcolepsy," J. Rheumatol., 20(5): 888-9, 1993.

11. Duteil, J.; Rambert, F. A.; Pessonnier, J.; Hermant, J. F.; Gombert, R.; Assous, E.; "Central alpha 1-adrenergic stimulaiton in relation to the behavior stimulating effect of modafinil; studies with experimental animals," Eur. J. Pharmacol., 180(1): 49-58, 1990.

12. Ferraro, L.; Tanganelli, S.; O'Connor, WT; Antonelli, T.; Rambert, F., "The vigilance promoting drug modafinil decreases GABA release in the medial preoptic area and in the posterior hypothalamus of the awake rat: possible involvement of the serotonergic 5-HT3 receptor," Neurosci. Lett., 220(1): 5-8, 1996.

13. Ferraro, L.; Tanganelli, S.; O'Connor, W. T.; Antonelli, T.; Rambert, F.; Fuxe,K., "The vigilance promoting drug modafinil increases dopamine release in the rat nucleus accumbens via the involvement of GABAergic mechanism," Eur. J. Pharmacol., 306(1-3): 33-9, 1996.

14. Gold, L. H., Balster, R. L., "Evaluation of the cocaine-like discriminative stimulus effects and reinforcing effects of modafinil," Psychopharmacology-Berl., 126(4): 286-92, 1996.

15. Griffiths, R. R.; Bigelow, G. E., and Henningfield, J. E., in Advances in Substance Abuse (Vol. 1), JAI Press Inc., pp. 1-90, 1980..

16. Jasinski, D. R.; Johnson, R. E.; and Henningfield, J. E.; "Abuse liability assessment in human subjects," TIPS, 196-200, 1984.

17. Johansson, C. E. and Balster, R. L., "A summary of results of a drug self-administration study using substitution procedures in rhesus monkeys," Bull. Narcotics, 30:43-54, 1978.

18. Laffont, F.; Agar, N.; Mayer, G.; Minz, M.; "Effect of modafinil in narcoleptic patients. Electrophysiologic and psychometric studies," Neurophysiol.-Clin., 25(2):84-95, 1995.

19. Laffont, F.; Mayer, G.; Minz, M.; "Modafinil in diurnal sleepiness. A study of 123 patients," Sleep, 17 (8 suppl); S113-5, 1994.

20. Lafon, L. "(-)-Benzhydylsulfinylacetamide," Procede de Preparatopm et Utilization en therapeutique," Eur. Patent 233106 A1, 1988, 13 pp.

21. Lafon, L., "Aryldisubstituted derivatives of acetamide, useful as stimulants and antidepressants, and medicaments containing them," Fr. Demande FR 2,601,673, 1988, 24 pp. (CA 109: 190043).

22. Lagarde, D.; Batejat, D.; Van-Beers, P.; Sarafian, D.; Pradella, S.; "Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment," Fundam-Clin-Pharmacol., 9(3):271-9, 1995.

23. Lagarde, D.; Milhaud, C.; "Electroencephalographic effects of modafinil, an alpha-1-adrenergic psychostimulant, on the sleep of rhesus monkeys," Sleep, 13(5): 441-8, 1990.

24. Lamberg, L., "Narcolepsy researchers barking up the right tree," JAMA, 276(10): 765-6, 1996.

25. Lin, J.S.; Hou, Y.; Jouvet, M., "Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat," Proc. National Acad. Sci., U.S.A., 93(24): 14128-33, 1996.

26. Lyons, T. J., French, J.; "Modafinil: the unique properties of a new stimulant," Aviat. Space Environ. Med., 62(5): 432-5, 1991.

27. Mignot, E.; Nishino, S.; Guilleminault, C.; Dement, W.C.; "Modafinil binds to the dopamine uptake carrier site with low affinity," Sleep, 17(5): 436-7, 1994.

28. Mitchell, P. B., "Novel French antidepressants not available in the United States," Psychopharmacol. Bull., 31(3): 509-19, 1995.

29. Moachon, G., Matinier, D., "Simultaneous determination of modafinil and its acid metabolite by high-performance liquid chromatography in human plasma," J. Chromatogr. Biomed. Appl., 654(1): 91-6, 1994.

30. Nicolaidis, S.; De Saint Hilaire, Z., "Nonamphetamine awakening agent modafinil induces feeding changes in the rat," Brain Res. Bull., 32(2): 87-90, 1993.

31. Panckeri, KA; Schotland, HM; Pack, AI; Hendricks, JC, "Modafinil decreases hypersomnolence in the English bulldog, a natural animal model of sleep-disordered breathing," Sleep, 19(8): 626-31, 1996.

32. Pierard, C.; Satabin, P.; Lagarde, D.; Barrere, B., Guezennec, C. Y., "Effects of a vigilance-enhancing drug, modafinil, on rat brain metabolism: a 2D COSY 1H-NMR study," Brain Res., 693(1-2): 251-6, 1995.

33. Roth, T.; Roehrs, T.A., "Etiologics and sequelae of excessive daytime sleepiness," Clin. Ther., 18(4): 562-76, 1996.

34. Saletu, B.; Saletu, M.; Grunberger, J.; Frey, R.; Anderer, P.; Mader, R., "Treatment of the alcoholic organic brain syndrome: double-blind, placebo-controlled clinical, psychometric and electroencephalographic mapping studies with modafinil," Neuropsychobiology, 27(1): 26-39, 1993.

35. Saletu, B.; Saletu, M.; Grunberger, J.; Frey, R.; Zatschek, I.; Mader, R.; "On the treatment of the alcoholic organic brain syndrome with an alpha-adrenergic agonist modafinil: a double-blind, placebo-controlled clinical, psychometric and neurophysiological studies," Prog. Neuropsychopharmacol. Biol. Psychiatry, 14(2): 195-214, 1990.

36. Shelton, J.; Nishino, S.; Vaught, J.; Dement, W. C.; Mignot, E., "Comparative effects of modafinil and amphetamine on daytime sleepiness and cataplexy of narcoleptic dogs," Sleep, 18(10): 817-26, 1995.

37. Simon, P.; Hemet, C.; Costentin, J., "Analysis of stimulant locomotor effects of modafinil in various strains of mice and rats," Fundam-clin-Pharmacol., 10(5): 431-5, 1996.

38. Simon, P., Hemet, C.; Ramassamy, C.; Costentin, J., "Non-amphetaminic mechanism of stimulant locomotor effect of modafinil in mice," Eur. Neuropsychopharmacol., 5(4): 509-14, 1995.

39. Simon, P.; Panissaud, C.; Costentin, J.; "The stimulant effect of modafinil on wakefulness is not associated with an increase in anxiety in mice. A comparison with dexamphetamine," Psychopharmacology-Berl., 114(4): 597-600, 1994.

40. Tanganelli, S.; Ferraro, L.; Bianchi, C.; Fuxe, K.; "6-Hydroxy-dopamine treatment counteracts the reduction of cortical GABA release produced by the vigilance promoting drug modafinil in the awake freely moving guinea-pig." Neurosci. Lett., 171(1-2): 201-4, 1994.

41. Tanganelli, S.; Fuxe, K.; Ferraro, L.; Janson, A.M.; Bianchi, C.; "Inhibitory effects of the psychoactive drug modafinil on gamma-aminobutyric acid outflow from the cerebral cortex of the awake freely moving guinea pig. Possible involvement of 5-hydroxytryptamine mechanisms," Naunyn-Schmiedebergs-Arch. Pharmacol., 345(4): 461-5, 1992.

42. Tanganelli, S.; Perez de la Mora, M.; Ferraro, L.; Mendez-Franco, J.; Beani, L.; Rambert, F.A., Fuxe, K.; "Modafinil and cortical gamma-aminobutyric acid outflow. Modulation by 5-hydroxytryptamine neurotoxins," Eur. J. Pharmacol., 273(1-2): 63-71, 1995.

43. Touret, M.; Sallanon-Moulin, M.; Fages, C.; Roudier, V.; Didier-Bazes, M.; Roussel, B.; Tardy, M.; Jouvet, M. "Effects of modafinil-induced wakefulness on glutamine synthetase regulation in the rat brain," Brain Res. Mol. Brain Res., 26(1-2): 123-8, 1994.

44. Touret, M.; Sallanon-Moulin, M.; Jouvet, M., "Awakening properties of modafinil without paradoxical sleep rebound: comparative study with amphetamine in the rat," Neurosci. Lett., 189(1): 43-6, 1995.

45. Ueki, A.; Rosen, L.; Andbjer, B.; Finnman, U. B.; Altamimi, U.; Janson, A.M.; Goldstein, M.; Agnati, L.F.; Fuxe, K.; "The vigilance-promoting drug modafinil counteracts the reduction of tyrosine

hydroxylase immunoreactivity and of dopamine stores in nigrostriatal dopamine neurons in the male rat after a partial transection of the dopamine pathway," Exp. Brain Res., 93(2): 259-70, 1993.

46. Woolverton, W.L., and Nader, M.A, in: M.W. Adler and A. Cowan (Eds.) *Modern Methods In Pharmacology* (Vol 6), Wiley-Liss New York, pp. 165 -192, 1990,

Memorandum

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

Date December 23, 1997

From Cynthia McCormick, M.D. /S/
Director,
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

To Paul Leber, MD
Director,
Division of Neuropharmacological Drug Products

Subject: Modafinil Review of Abuse Liability

Enclosed is the final review of the Abuse Liability package for NDA 20-717 in response to your request for consultation.

APPEARS THIS WAY ON ORIGINAL

DIVISION OF ANESTHETIC, CRITICAL CARE
AND ADDICTION DRUG PRODUCTS

HFD-120 CONSULT
ABUSE LIABILITY ASSESSMENT

NDA #:	**20-717**
SPONSOR:	**CEPHALON, INC.**
PRODUCT:	**PROVIGIL®**
GENERIC NAME:	**MODAFINIL**
CHEMICAL NAMES:	**2-[(DIPHENYL,ETHYL)SULFINYL]-ACETAMIDE**
DOSAGE FORM:	**TABLET**
CLINICAL DOSAGES:	**100 mg, and 200 mg**
INDICATION:	**IMPROVE WAKEFULNESS IN PATIENTS WITH EXCESSIVE DAYTIME SLEEPINESS ASSOCIATED WITH NARCOLEPSY.**
REVIEWERS:	**BeLinda A. Hayes, Ph.D., Michael Klein, Ph.D., Silvia Calderon, Ph.D., Igor Cerny, Ph.D.**
REVIEWERS DATE:	**DECEMBER 16, 1997**

BACKGROUND.

Cephalon, Inc. has submitted NDA 20-717 for Modafinil tablets to Food and Drug Administration Division of Neuropharmacological Drug Products. Modafinil, PROVIGIL®, is indicated for the improvement of wakefulness in patients with excessive sleepiness associated with narcolepsy. PROVIGIL® will be marketed as 100 and 200 mg tablets. The maximum recommended daily dose is 400 mg.

According to 21CFR ¶ 314.50 (5)(vii), FDA requires the sponsor to submit an abuse liability assessment package and scheduling proposal with their NDA submission when developing a new pharmaceutical product, which demonstrates a similar pharmacological profile and/or structural similarity with a known drug of abuse. In accordance to the Controlled Substances Act (CSA) Modafinil meets the requirements for abuse liability assessment. Issues relating to abuse liability and the appropriate scheduling of the drug under the CSA are the responsibilities of the Division of Anesthetic, Critical Care, and Addiction Drug Products' Controlled Substance Evaluation Team. Evaluation of the compound's chemical, pharmacological (both preclinical and clinical), pharmacokinetic, and pharmcodynamic profiles of the compound, and the adverse effects associated with the compounds are the basis of the abuse liability assessment.

In reviewing the abuse potential of Modafinil, the following factors were considered:

- **Binding Profile.** Results from *in vitro* binding studies which demonstrated that modafinil was active at the dopamine reuptake site and that it displayed some affinity for the dopamine receptors. Modafinil was approximately 100-fold less potent than cocaine in stimulating the release of ^{3}H-dopamine.

- **Reinforcing Efficacy.** Modafinil functions as a positive reinforcer, as evidenced by its ability to maintain self-administration behaviors in primates trained to self-administered cocaine. This behavioral profile is a major preclinical indicator that a drug is likely to possess abuse potential and that it will produce psychological and/or physical dependence.

- **Discriminative Stimulus Properties.** In preclinical drug discrimination studies, modafinil only partially generalized to the discriminative stimulus effects of cocaine and d-amphetamine.

- **Psychoactive Properties.** Modafinil produces psychoactive and euphoric effects, alteration in mood, perception, thinking and feelings typical of other scheduled CNS stimulants.

- **Pharmacokinetic Profile.** Modafinil has a quick onset and short duration of action. Drugs with this profile are considered to have a greater likelihood of being abused.

- [redacted]

- **Chemical Properties.** Modafinil lacks water solubility and decomposes with heat, and therefore would not likely be abused by parenteral, intranasal, or inhalation routes, as are cocaine, methylphenidate, and amphetamine.

- **Potency Relative To Other CNS Psychostimulants.** Relative potency differences between modafinil and other CNS pyschostimulants are significant. Although in primates modafinil functioned as a positive reinforcer at doses 22- and 66-fold lower than the proposed therapeutic dose (400 mg/day; 6.67 mg/kg), it is considerably less potent than amphetamine and methylphenidate.

- **CNS Stimulants.** Relative differences between modafinil and other CNS psychostimulants are significant. Although in primates modafinil functioned as a positive reinforcer at doses 22- and 66-fold lower than the proposed therapeutic dose (400 mg/day; 6.67 mg/kg), it is considerably less potent than amphetamine and methylphenidate.

- Diversion. As a CNS psychostimulant, its diversion from pharmacies, hospitals, and physicians' offices for purposes of abuse would be considered a likely

prospect.

Off-Label Use. Although modafinil has not been studied in children, its use in the treatment of attention deficit disorder in children is possible. Its use for other off-label applications including as an aid in weight loss or performance enhancement are possible.

PRECLINICAL PHARMACOLOGY

Biochemical Profile. The precise biochemical mechanism by which modafinil elicits its wake-promoting effects has not been clearly elucidated. Available data suggest that modafinil does not act directly on any single neurotransmitter system, but rather, modafinil appears to indirectly affect dopaminergic, serotonergic, and GABA systems, or a combination of these systems and requires an intact α_1-adrenergic system. The drug's effect on the dopaminergic system appear to be mediated by the ability to modulate GABA-ergic transmission. Using microdialysis in the nucleus accumbens, modafinil (30, 100, and 300 mg/.kg, s.c.) dose-dependently increased the release of dopamine while decreasing the release of GABA in rats. Local infusions of the $GABA_B$ antagonist phaclofen and the $GABA_A$ agonist muscimol, and the GABA reuptake inhibitor SKF589976A decreased modafinil-induced release of dopamine from the nucleus accumbens. In contrast, the $GABA_B$ agonist baclofen increased the modafinil-induced release of dopamine.

The affinity of modafinil for various receptors has been evaluated in the *Nova Screen*, an *in vitro* radiolabelled binding study screen. Results demonstrated that modafinil (0.1 mM) does not inhibit more than 37% of the binding to any of the panel of receptors tested. These included the following types of sites: adenosine, adrenergic, benzodiazepine, dopamine (non-selective), $GABA_A$ and $GABA_B$, glutamate ((AMP, kainate, NMDA, glycine site, and MK-801), strychnine-sensitive glycine, histamine (H1, and H2), muscarinic (non-selective, central and peripheral), nicotinic, 5-HT, sigma, opiate (nonselective), ion channels (i.e., calcium channel (L and N), chloride, potassium channel (ATP sensitive, voltage sensitive and insensitive)), NE and 5-HT uptake/transporter, and second messengers systems (adenylate cyclase, inositol triphosphate, and protein Chinese C).

Modafinil (0.1mM) displayed some binding affinity for the dopamine receptors; and it showed 100% inhibition of dopamine uptake (IC_{50} = 3.10 μM; K_i = 1.93 μM). Modafinil also lacked affinity for the A_1 or A_2 adenosine receptors. Modafinil (0.001 - 10.0 μM) did not inhibit the binding of [^{3}H[]DPCPX (A_1 receptors) or [^{3}H]CGS-21680 (A_2 receptors) to the adenosine receptors in whole brain membrane preparations (except cerebellum).

In a second set of studies, the affinity of modafinil for various uptake sites was evaluated. These studies included evaluation of norepinephrine (^{3}H-desipramine in rat cortex), serotonin (^{3}H-Citalopram) and dopamine (^{3}H-mazindol in rat striatum, and ^{3}H-WIN in guinea pig striatum) uptake sites. Except for binding at the dopamine uptake site, binding inhibition was not obtained. In radioreceptor studies using ^{3}H-mazindol, the affinity of modafinil for the dopamine uptake site was approximately five-fold lower than affinity of cocaine, 16-fold lower than d-amphetamine, 30- and 60-fold lower than the affinity shown by nomifensine and GBR-12909 [K_i (nM): 2,050 ± 30, vs. 375 ± 28 for cocaine; 132 for d-amphetamine; 68 ± 10 for nomifensine, and 24 ± 5.6 for GBR 12909 (Table I)].

TABLE 1. EFFECT OF MODAFINIL ON DOPAMINE (DA), SEROTONIN (5HT), AND NOREPINEPHRINE (NE) UPTAKE.

COMPOUND	K1 (nM) INHIBITION OF ^{3}H-MAZINDOL BINDING	IC_{50} (nM) INHIBIT DA UPTAKE		IC_{50} (nM) INHIBIT DA UPTAKE
	Striatum	Striatum	Cortex	Cortex
GBR 12909	24	-	-	-
Nomifensine	68	89	47	24
d-Amphetamine	132 (K_H); 29,400 (K_L)	-	-	-
Cocaine	375	IC50 5-Fold greater than nomifensine	-	-
Modafinil	2050	6,800	6,500	8,300
Modafinil acid	-	>1,000,000	66,000	15,000
Modafinil sulfone	-	>500,000	68,000	2,800

The ability of modafinil to affect the release of dopamine was examined in both mouse and rat striatum. The effects of modafinil to stimulate the release of [^{3}H]DA from mouse striatum was compared with that of d-amphetamine. In contrast to observations with d-amphetamine (10 μM), modafinil (10 μM) did not stimulate [^{3}H]-dopamine from the synaptosomes. In rat striatal slices preloaded with ^{3}H-dopamine, the ability of modafinil (300.0 μM), cocaine (3.0 -30.0 μM), d-amphetamine (3.0 - 30.0 μM), and nomifensine (30.0 - 300.0 μM) to increase spontaneous and electrically-evoked release of dopamine was evaluated. Under basal conditions, modafinil was less potent than nomifensine (10.0 and 30.0 μM) and cocaine (3.0 and 10.0 μM) in stimulating [^{3}H[-dopamine release. Using electrical stimulation to stimulate the release of [^{3}H]-dopamine from rat striatal slices, modafinil was less potent than nomifensine (10.0 and 30.0 μM) and cocaine (10.0 μM) in blocking the release of [^{3}H]-dopamine following electrical stimulation. Results from these studies indicated that modafinil was approximately 100-fold less potent than nomifensine or cocaine in stimulating the release of ^{3}H-dopamine.

Although dopamine uptake inhibition or stimulation of dopamine release is believed to be an important property of most amphetamine-like stimulants, the implication of the low affinity shown by modafinil for dopamine uptake sites and the negligible affinity for other receptor systems in the psychopharmacological profile of modafinil is unknown. The hypothesis currently espoused regarding the mechanism of action of modafinil is that stimulation of α-1 adrenergic sites are involved. This is based on the observation that the modafinil induced increase in motor activity in mice is antagonized by central α1-antagonists such as prazosin, but not by dopamine antagonists, although modafinil does not bind to α1-receptors *in vitro* at concentrations up to 10.0 μM, using [^{3}H]-prazosin in canine cortical membranes.

Pharmacological Profile. Modafinil was studied preclinically for effects on arousal and locomotor activity. In rats, the effects of modafinil on wakefulness were compared to that of methamphetamine. Modafinil (30.0 - 300.0 mg/kg) promoted EEG-defined wakefulness in a dose-dependent manner. Modafinil was less potent than methamphetamine in inducing a state of wakefulness; a dose of 300.0 mg/kg of modafinil was equipotent to 1.0 mg/kg of methamphetamine. In contrast to methamphetamine, modafinil did not produce an increased drive for compensatory sleep (i.e., NREM). In another study, the effects of modafinil (64.0 and 128.0 mg/kg, i.p.) and d-amphetamine (2.5 and 5.0 mg/kg, i.p. on sleep/waves cycles (duration), slow wave sleep (SWS), paradoxical sleep (PS), and wakefulness were evaluated in Sprague Dawley rats (Touret *et al.*, 1995). Both modafinil and d-amphetamine dose-dependently increased wakefulness; modafinil was approximately 51-times less potent than d-amphetamine. Similar effects were seen with 128.0 mg/kg modafinil and 2.5 mg/kg d-amphetamine. d-Amphetamine wakefulness was followed by recovery of lost PS rebound on the day of administration, whereas modafinil did not produce this effect. In contrast to d-amphetamine, modafinil did not affect the sleep patterns of the rats one day post-treatment. In modafinil-treated rats, sleep pattern on post-injection day was similar to that of controls, while that of d-amphetamine-treated rats was modified.

The effects of modafinil on arousal were also evaluated in sleep deprived rats. Results from this study demonstrated that modafinil was effective in reducing preexisting sleep deficit brought on by forced wakefulness and the accumulation of additional REM sleep debt incurred during sleep deprivation. When modafinil (100.0 mg/kg) was administered to rats deprived of sleep for six hours, modafinil prolonged EEG-defined wakefulness without increasing NREM and REM recovered after the extended period of sleep deprivation was reduced by modafinil. Modafinil at a dose of 300.0 mg/kg did not alter levels of sleep, wakefulness, or locomotor activity two days post-treatment.

In another rat study, effects of modafinil on sleep/wake cycles were examined in anesthetized rats. Modafinil (32.0 to 250.0 mg/kg) increased the duration of wakefulness and the latency to the first appearance of REM sleep in a dose-dependent manner. The SWS was also decreased in a dose-dependent manner. Modafinil (64.0 and 128.0 mg/kg) and d-amphetamine (2.5 and 5.0 mg/kg) produced similar results on recovery of paradoxical sleep in rats implanted with electrodes. Modafinil and d-amphetamine each cause dose-dependent increases in wakefulness. In contrast to d-amphetamine, the wakefulness induced by modafinil was not followed by recovery of lost paradoxical sleep.

Effects of modafinil on sleep and wakefulness were examined in two standard dog models. In the English bulldog model of hypersomnolence, the effects of modafinil (10.0 mg/kg, i.v.) on sleep (parameters measured included total sleep time; sleep latency (total minutes till onset of NREM); sleep disorders breathing index; and wakefulness were evaluated. Modafinil significantly ($p \leq 0.005$) produced marked wakefulness and increased sleep latency (346 $\pm$ 105 min for modafinil vs 71 $\pm$ 40 min for vehicle control). In the doberman narcoleptic model, the effects of modafinil (0.125 - 10.0 mg/kg, i.v.) and d-amphetamine (2.5 - 200.0 mg/kg, i.v.) on cataleptic sleep, locomotor activity, and cardiovascular parameters were examined. Modafinil at a dose of 10.0 mg/kg and 200 mg/kg of d-amphetamine showed equal efficacy in increasing wakefulness and decreasing sleep in both normal and narcoleptic dogs. Unlike d-amphetamine, modafinil significantly reduced REM in both normal and narcoleptic dogs. Modafinil, up to 10.0 mg/kg, had no effects on suppressing or deceasing cataplexy.

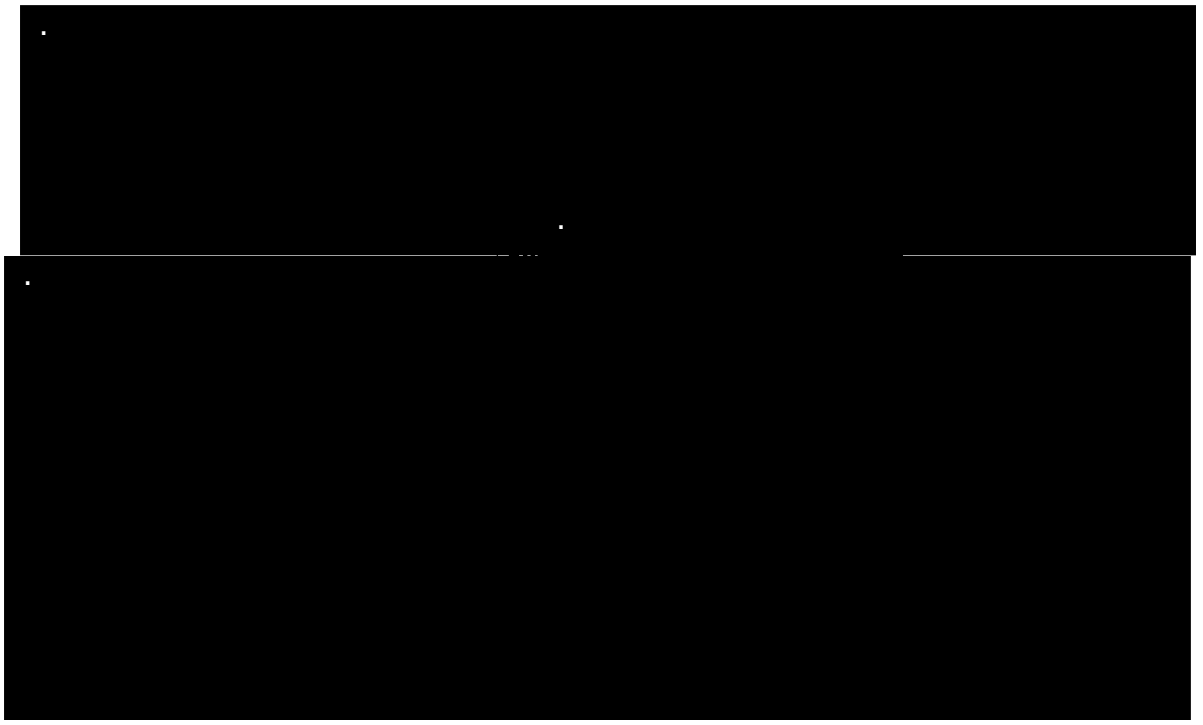
CHEMISTRY

Modafinil is a white to off-white crystalline powder that is practically insoluble in water (10mg/100 mL) and cyclohexane, slightly soluble in ethanol (1 mg/mL). It is sparingly to slightly soluble in methanol (10 mg/mL) and acetone.

[redacted]

Modafinil and its analog Adrafinil can be purchased without any restriction through the Internet. Both drugs are advertized as "smart drugs" which promote vigilance and alertness. Modafinil is approximately ten-fold more expensive than adrafinil: Modafinil, Modiodal, 100 mg, $640 per 120 tablets; Adrafinil, Olmifon, 300 mg, $22 per 40 tablets).

[redacted]



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PHARMACOKINETICS PROFILE IN HUMANS

Issues of pharmacokinetics which relate to abuse liability of modafinil are summarized below. Data is based on information in the NDA and the pharmacokinetics review.

Modafinil is well-absorbed after oral administration. Peak plasma concentration occurred at 1 to 4 hours. Elimination half-life was 9 to 14 hours after a single oral dose of 200 or 400 mg. Both modafinil and modafinil acid exhibited linear pk over a dose range of 50-499 mg. Oral bioavailability of a 200 mg tablet relative to a micronized aqueous suspension was close to 100%. Apparent volume of distribution of modafinil was larger than the volume of total body water (0.6 L/kg). Females (35%) appeared to excrete less modafinil acid in urine than males (51%). Clearance of modafinil in males decreased slightly (approximately 10-20%) as the age increased. Stereospecific pk of enantiomers have been demonstrated. The dextro-isomer was eliminated faster (100-140 mL/min) than the levo-isomer (35-50 mL/min).

Modafinil was extensively metabolized after oral dosing by deamination, oxidation, and aromatic ring hydroxylation. Total oral clearance of modafinil after a single dose was approximately 60 mL/min. Less than 10% of the dose was excreted in urine as parent drug. Modafinil acid accounted for 50-60% of the dose in males and 30-40% in females. Urinary excretion of modafinil sulfone was negligible. Renal clearance of modafinil accounts for 5-6% of plasma clearance, indicating that modafinil is primarily eliminated by liver metabolism. After a single dose of side-chain labeled [redacted]C-modafinil, 79.6 ± 5.9% and 1.0 ± 0.3% of the dose was recovered in urine and feces, respectively, over 11 days.

After multiple once daily 200, 400, and 600 mg dosing, apparent steady-state plasma levels were reached after 2-4 days of dosing. Elimination half-life after the last dose of multiple dose regimen was 13-18 hours. Modafinil was moderately bound to plasma proteins (61-65%), essentially to albumin.

Food delayed absorption of modafinil (Tmax: 3.21 vs. 2.05 hours). However, AUC & elimination half-lives did not differ between fasted and fed conditions. In patients with renal impairment, elimination of modafinil acid was reduced after a single dose of 200 mg. Only 25% of the modafinil dose was excreted in urine as modafinil acid in patients with renal insufficiency. Forty-five percent of the modafinil dose was excreted as modafinil acid in the urine of healthy subjects.

In a multiple dose study (200 mg/day) for 8 days in patients with liver cirrhosis, patients exhibited high modafinil AUC and extended half-life, suggesting that the major elimination route of modafinil was liver.

In a single-dose pk interaction study with methylphenidate and modafinil, no clinically important alterations in the pk profile of either drug was noted. A delay in oral absorption of modafinil was observed (Tmax of 2.9 vs. 1.9 hours).

An open label, multiple dose, pk study in elderly male and female volunteers followed administration of 300 mg modafinil per day for 7 days. Plasma levels were determined on days 1 & 7. Maximum plasma concentrations after the first dose were much higher than previous study in healthy young volunteers. Plasma levels of modafinil obtained from day 7 were higher than those of day 1, implying accumulation after 7 days of daily dosing of 300 mg modafinil in elderly subjects.

The pk portions of the pivotal Phase III efficacy trials were designed to evaluate the steady state plasma trough levels of modafinil and the two metabolites, modafinil acid and modafinil sulfone. After daily doses of 200 mg modafinil, plasma trough levels of modafinil and the two metabolites reached steady state by Week 3 and remained unchanged through Week 9. After

daily doses of 400 mg modafinil, the plasma trough levels of modafinil at Week 9 were significantly lower (approximately 20%) than those of Week 3. The two metabolites did not show this difference. Also, the plasma trough levels of modafinil sulfone were negatively correlated with age, suggesting metabolism of modafinil to modafinil sulfone might be slower in older patients. Also, plasma levels of modafinil sulfone from female patients in the 400 mg group were higher than those of male patients at Weeks 3 and 6.

CLINICAL TRIALS

Issues related to abuse liability of modafinil from the clinical trials are summarized below. Data was derived from the medical review of the NDA and the Integrated Summary of Safety.

Modafinil has been studied in adult (17-65 yrs) patient populations, for use in treatment of narcolepsy in a dosage of 200-400 mg/day. No study has been specifically designed to evaluate the metabolism, safety, or efficacy of modafinil in geriatric or pediatric patients with narcolepsy.

Safety and efficacy were assessed in two 9 week placebo-controlled, double-blind, randomized, parallel-group study of safety & efficacy of 200 mg and 400 mg of oral modafinil in patients with narcolepsy followed by a 40 week, open-label, flexible-dose continuation study with and without a 2 week discontinuation segment between the blinded and open label parts of the study.

The protocol called for 3 groups of 95 patients each to be randomly assigned to 1 of 3 treatment arms. Approx. 15 patients are to be randomized at each of the 20 sites during a 6 month enrollment period. Eligible patients receive a specified number of tablets to be taken daily for 9 consecutive weeks. Of 285 patients randomized, 283 (99%) received study medication and were considered to be evaluable for the safety analyses. Two were not evaluable. One patient was discontinued soon after due to a history of illicit drug use and a positive urine drug screen the patient did not report medication use, but when it was returned there were 12 tablets missing. The database did not include study medication of AE data (other than a note stating patient did not have any AES)(0.35% possible drug abuse in clinical trial). The other patient was discontinued when the investigator determined that the patient did not meet inclusion criteria. Fourteen patients (15%) in the modafinil 400 mg group discontinued study compared to 3 patients (3%) in the modafinil 200 mg group and 5 patients (5%) in the placebo treatment group. Eleven of 14 patients who discontinued from modafinil 400 mg group did so because of AE's. None of the patients in the placebo group and 1 patient in the modafinil 200 mg group discontinued for AE's. During the study the blind for Patient 1403 was broken by the investigator because of concerns that the patient had taken another CNS stimulant.

Patient Distribution/Disposition:

Of the 273 patients randomized, 271 (99%) received medication and were valuable for safety analyses. Two patients were not evaluable for safety or efficacy analyses. Patient 0907 (Mod 400) & Patient 1205 (mod 200 mg) were randomized prior to receiving results of the baseline urine drug screen (UDS) and were instructed not to begin taking study medication until cleared for entry. Both patients had positive UDS results and returned all study medications unopened. Approximately 50% of the patients in each treatment arm reported light to moderate use of caffeine. Half in each treatment group reported light to moderate alcohol use.

Patients in modafinil 400 mg treatment group were able to stay awake for a significantly longer time at endpoint on the MWT compared to patients in placebo treatment group. More patients in the Modafinil 400 mg treatment group had clinical improvement in symptoms based on the CGI-C when compared to patients on placebo. Patients in the mod 400 & mod 200 treatment groups could stay awake significantly longer as measured by all parameters of MWT, except

REM Sleep Latency, when compared to patients on placebo. Patients in both active treatment groups exhibited statistically significantly higher Average Sleep Latency values compared to patients in the placebo group at Weeks 3,6 & 9, and at Endpoint ($p < 0.001$). Mod 400 vs mod 200 was not significant for MWT average sleep latency at any time point.

On average, patients in the mod 400 group exhibited lower Total Sleep Time (8.11 min.) than patients on placebo (9.92 min) at Endpoint. Patients in the mod 200 group exhibited lower Total Sleep Time (7.88 min) than either high dose or placebo patients.

Patient Subjective Evaluation of Sleep Latency: Patients in both active treatment groups had significantly greater improvement than patients on placebo at each visit. A greater percentage of patients treated with modafinil 100 mg showed improvement (64%) compared to patients in the placebo group (36%) at Week 1 ($p < 0.001$).

Other Clinical Trials demonstrated a comparative decrease in excessive daytime somnolence by 80% for modafinil 400 mg, 66% on modafinil 200 mg and 34% for subjects on placebo.

Efficacy Summary:

Patients were asked to provide subjective responses by estimating how long they were able to stay awake at the end of each test period. Modafinil 400 mg, 200 mg and combined treatment groups all exhibited significantly more patients reporting staying awake at Endpoint than patients in the placebo group ($p < 0.050$). Patients in both active treatment groups had significantly greater improvement than patients in the placebo group at each visit. Patients in the modafinil 400 mg treatment group had significantly greater improvement than patients in the modafinil 200 mg treatment group only at Weeks 3 and 6. No significant differences were found between the 2 active treatment arms.

Higher numbers of patients in the 2 active treatment groups, compared to patients in the placebo group, responded positively to questions regarding "feelings about life as a whole", "quality of life during the past week", "general health", "social functioning", "productivity", "bodily pain", and "driving capability". None was reported statistically.

Discontinuation evaluations of Segment II at end of Weeks 10 & 11 include recording of concomitant meds and AE's. At end of Week 11, patients also complete the same and as baseline data for the Open Label Phase, urine drug screen modafinil plasma level, QOLIN (Quality of Life in Narcolepsy) patient inventory and CGI-S (global inventory).

Effect of modafinil treatment is assessed by analyzing change from Week 9 to 11 within modafinil dose groups, and by comparing modafinil/placebo patients to placebo/ placebo patients at Week 11.

DEATHS, DRUG OVERDOSES, ADVERSE EVENTS

Five deaths were included in the clinical studies by modafinil-treated subjects. These were from the foreign sponsored studies. Causes of death were primarily "asthenia" or "myocardial infarction" (Table 2).

Table 2. Deaths: All studies.

Study	Subject	Dose (mg/d)	Duration of therapy (d)	AEs preceding death	Severity	Relatedness
MOD-032	40 yr F (ALS)	200	Unknown	Aggravation Reaction	Severe	Not related
MOD-035	82 yr F (Depression)	150	1	Heart failure, Pain, Kidney Function Abnormality, Flatulence	Life-threatening	Not related
Open/2-1	65 yrs F (major depressive episode)	200	unknown	syncope, dyspnea	Life-threatening	Unknown
P1439	68 yrs F (Age assoc. Memory impairment	400	unknown	Asthenia*	Unknown	Unknown
MOD-021**	58 yrs M (major depressive episode)	200	8	Aggravation of encephalopathy	NE	Not related***

* Database indicated asthenia at cause of death; actual cause of death was MI.

** Subject death not listed in database; information obtained from narrative.

***Narrative indicated that "advanced cirrhosis of liver could be totally responsible for outcome."

PRECLINICAL ABUSE LIABILITY ASSESSMENT

The abuse potential of modafinil was evaluated in rats and primates. Its abuse potential profile was examined in the following preclinical studies:

- **Study Report Nº DRR-96-07:** Abuse Potential Evaluation of Modafinil: I Drug Discrimination in Cocaine Trained Rats II. Drug Self Administration In Cocaine Trained Rhesus Monkeys III. Drug Discrimination In Amphetamine Trained Rats. These studies were performed under contract by Dr. Robert L. Balster at the Center for Drug and Alcohol Studies, Virginia Commonwealth University.
- **Study Report Nº DRR-96-2:** Study of the addictive properties of modafinil by intravenous drug self-administration. This study was performed at the laboratory of Professor Michel LeMoal at the INSERM.
- **Study Report Nº DRR-96-18:** Study of the addictive potential of modafinil by drug-induced place conditioning. This study was performed at the laboratory of Professor Michel LeMoal at the INSERM.

Study Report Nº DRR-96-07: **Abuse Potential Evaluation of Modafinil: I Drug Discrimination in Cocaine Trained Rats II. Drug Self Administration In Cocaine Trained Rhesus Monkeys III. Drug Discrimination In Amphetamine Trained Rats.**

Objective: To evaluate the discriminative stimulus and reinforcing effects of modafinil in rats and primates, respectively.

DISCRIMINATIVE STIMULUS EFFECTS IN COCAINE-TRAINED RATS. The discriminative stimulus properties of modafinil were evaluated in rats trained to discriminate cocaine (10 mg/kg, ip) from saline in a 2-lever operant procedure under a fixed-ratio (FR) 32 schedule of reinforcement during daily 30-min sessions. After criterion (greater than 85% correct-lever responding and the first consecutive 32 responses on the correct lever on the previous training day) was established, substitution tests were conducted. On substitution test sessions, doses of modafinil (3.0-250 mg/kg; 30 min pretreatment time), d-amphetamine (0.1-3.0 mg/kg, 10 min pretreatment time), or l-ephedrine (3.0 - 30.0 mg/kg, 10 min pretreatment time) were administered prior to the behavioral session. To assess the role of the adrenergic system in the discriminative stimulus effects of modafinil, an antagonist test session with prazosin was conducted after the substitution test sessions were completed. During the antagonism test, prazosin (0.3 mg/kg) alone or prazosin (0.3 mg/kg) 10 min prior to 250 mg/kg of modafinil was evaluated. The behavioral session was conducted 30 minutes after the subjects received the modafinil injection and 40 minutes after they received prazosin only. Results from the study are shown in figure 1 (as copied from the sponsor's submission). Both d-amphetamine and l-ephedrine dose-dependently substituted for the stimulus cue of cocaine. The highest dose of d-amphetamine tested elicited 100% cocaine-lever responding; whereas the highest dose of l-ephedrine tested only elicited approx. 80% cocaine-appropriate responding and this was associated with marked behavioral disruption (i.e., a substantial decrease in rate of responding).

When 3-100 mg/kg of modafinil was substituted for cocaine, the subjects responded exclusively on the saline lever. Cocaine-appropriate responding was observed when 150 and 250 mg/kg of modafinil was tested. Modafinil, at a dose of 150 mg/kg, only substituted for cocaine in one out of six rats tested elicited; 4 out of 6 rats elicited cocaine-lever responding at a dose of 250 mg/kg. However, this high dose tested also reduced rates of responding by 59% when compared to the control response rate.

The results from the antagonism test with 0.3 mg/kg prazosin alone and in combination with 250 mg/kg of modafinil are presented in figure 2 (copied from the sponsor's submission). Prazosin (0.3 mg/kg) alone elicited exclusively saline-appropriate responding. When 0.3 mg/kg prazosin was administered 10 minutes prior to 250 mg/kg modafinil, prazosin failed to attenuate either the cocaine-like discriminative stimulus effects or the response rate effects of this dose of modafinil.

DISCRIMINATIVE STIMULUS EFFECTS IN AMPHETAMINE-TRAINED RATS. The discriminative stimulus properties of modafinil were evaluated in rats trained to discriminate d-amphetamine (1.0 mg/kg, ip) from saline in a 2-lever operant procedure under a fixed-ratio (FR) 32 schedule of reinforcement during daily 30-min sessions. After criterion (greater than 85% correct-lever responding and the first consecutive 32 responses on the correct lever on the previous training day) was established, substitution tests were conducted. Substitution test sessions were conducted with modafinil (10.0, 30.0, 100.0, and 250.0 mg/kg), and d-amphetamine (0.1, 0.3, 1.0 and 3.0 mg/kg)

d-Amphetamine dose-dependently substituted for the training dose (1.0 mg/kg) of d-amphetamine. Only saline-appropriate responding was observed when 10, 30, and 100.0 mg/kg of modafinil was substituted for d-amphetamine. Amphetamine-appropriate responding was elicited by 250.0 mg/kg of modafinil; only 51.4% d-amphetamine-lever responding was measured. However, a substantial decrease in rates of responding was observed and one rat died within 5 hours of modafinil administration.