

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020717

PHARMACOLOGY REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 7, 1997
FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products
TO: NDA 20-717
Provigil®, modafinil
100 or 200 mg tablets
Sponsor: Cephalon, Inc.
SUBJECT: Overview of Pharmacology and Toxicology

Provigil is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. The pharmacology/toxicology portion of this NDA is marginally acceptable to support an approvable action for this indication.

The mechanism by which modafinil promotes wakefulness has not been determined. It does not bind to the usual spectrum of receptors, nor does it appear to act as an adrenergic agonist or to affect norepinephrine release. Modafinil's effects are pharmacologically distinct from those of the CNS stimulants in that it promotes wakefulness without increased locomotor activity, aggressiveness or stereotypic behavior. In drug discrimination studies in rats and monkeys designed to examine its abuse potential, modafinil substituted for cocaine or d-amphetamine. It was not self-administered in drug-naive rats, however. The metabolic profile of modafinil is qualitatively similar across species, including humans. There are two major metabolites, the acid and the sulfone, neither of which possesses pharmacological activity. Modafinil induces its own metabolism through induction of hepatic enzymes. The effect is marked in the mouse, less in dog and rat, and occurs at doses of 400 mg or higher in humans.



Carcinogenicity

The 78 week mouse and 104 week rat bioassays were taken to the CAC-EC on March 11, 1997 (report attached). Doses of 6, 30 and 60 mg/kg/day were used in both studies. No increase in tumors occurred in the drug treated groups. It was recommended that the rat study would be acceptable, although the doses were marginal, based on an increase in the severity of spontaneous chronic progressive nephrosis in male rats, which led to an increase in mortality in that group. The mouse study was considered to be inadequate, however, in that a maximally tolerated dose was not reached. The sponsor was informed that an alternative *in vivo* assay might be an acceptable replacement or that the bioassay could be repeated using higher doses. In either case, it would be necessary for them to present a rationale for their choice to the full CAC. This was done on October 31, 1997 and a draft of that report is attached.

The Division worked with the Sponsor to select an appropriate alternative model. The choice was essentially limited to the TG.AC mouse, the only model for non-genotoxic compounds for which there is at least some experience. Modafinil is clearly non-genotoxic in an extended battery of tests which include the standard assays for mutagenicity and clastogenicity (*in vitro* and *in vivo*) as well as unscheduled DNA synthesis and cell transformation assay. The problem is that the TG.AC is a dermal application model, with skin as the primary target (forestomach and marrow also respond), and modafinil is an oral drug which is rapidly metabolized by the liver to two major metabolites. There is essentially no experience with the oral route in the TG.AC model. To address the issue of systemic exposure after dermal application the sponsor conducted an acute dermal study using two doses, 60 mg/kg (the high dose in the bioassay) and 360 mg/kg, in the parent strain of the TG.AC mouse. An oral dose group receiving 360 mg/kg was included. Plasma measurements were made of parent, modafinil acid and modafinil sulfone, at 1 and 4 hours, to determine if dermal exposures of parent and metabolites would be comparable to oral exposures. Although levels of both parent and metabolites were lower after dermal than after oral administration, especially the sulfone, the dermal route achieved reasonable exposures of all three moieties. The CAC unanimously agreed that the addition of a TG/AC assay to the standard rat bioassay would allow for adequate evaluation of the carcinogenic potential of modafinil. There was general agreement that it would be pointless to repeat the mouse bioassay at higher doses because the high degree of induction in that species makes it impossible to achieve adequate exposure to parent drug. The sponsor must now conduct a one month study to determine the appropriate doses and endpoints for the definitive TG.AC assay. When that study is completed, and the final protocol is submitted, the results will be taken to the CAC for concurrence with the dosage

selection and other details of the protocol (determination of target site exposure, use of appropriate solvent, etc.)

Reproduction studies

The sponsor has labeled modafinil Category B; we have changed it to C for two reasons: 1) a threshold dose for teratogenicity was established in the rat and 2) the segment I and II studies were conducted at inadequate doses to fully characterize the potential effects, in addition to the fact that they were non-GLP studies.

The reproductive toxicology studies for modafinil border on being unacceptable, with the exception of a peri- and post-natal study in rats which was conducted by Argus Laboratories in 1995 according to ICH guidelines. The fertility study in rats and the teratology studies in rats and rabbits, conducted by [REDACTED] in 1984 and 1985 were not carried out in compliance with Good Laboratory Practices Regulations, specifically lacking periodic and documented monitoring by an independent Quality Assurance Unit. I learned from our Scientific Investigations staff that we have an MOU with the French as of November, 1986 which defines the inspection process and acceptability of studies, but would not cover these studies. I was told that, in general, the quality of such studies has been low until the last 3 or 4 years. Irrespective of how the studies were conducted, they are clearly inadequate in terms of doses used to characterize potential effects. The only redeeming feature is that the rat teratology study establishes a threshold dose of 200 mg/kg (5 times the human dose on a body surface area basis) for teratogenic effects. Minimal fetal toxicity (resorptions, hydronephrosis, skeletal variations) was seen at that dose, in the absence of maternal toxicity. However, the ICH guideline, "Detection of Toxicity to Reproduction for Medicinal Products" clearly states (pages A-4 and A-5) that some minimal toxicity is expected to be induced in high dose dams, and it defines what endpoints are appropriate. Without appropriately high doses the studies do not adequately evaluate the full spectrum of potential effects on fertility or on the fetus.

The peri- and post-natal study referenced above is an adequate GLP study, but it has not yet been officially submitted to the Agency. In the process of reviewing the studies for this memo it came to my attention that the report for that study which was submitted to the NDA was labeled an interim report. It did not, therefore, contain any of the data to evaluate either reproductive performance of the F₁ (pups) generation or to evaluate the effects of the drug on behavioral parameters of the F₁ pups, assessment of learning and memory being a critical component of such a study. I telephoned the Sponsor on November 4, 1997, and they conceded that the final report had not been submitted. I received a desk copy (without plasma level data, which will not be available until December) on November 6, 1997, and on the basis of that am able to determine that no adverse effects occurred in that study at doses up to 200 mg/kg/day. It should be noted

that minimal maternal toxicity was achieved in this study, at a dose that did not cause toxicity in the segment II study, qualifying it as an acceptable study for peri- and post-natal evaluation. (The reason for the discrepancy with respect to maternal toxicity is not clear, but it may be due to better solubility in the solvent that was used - ORA-Plus instead of CMC. Modafinil is relatively insoluble in most solvents). That study was not designed to examine fetuses for teratogenic effects.

CONCLUSIONS

The sponsor will conduct, and submit during phase 4, a dermal TG.AC assay to replace the inadequate mouse bioassay. This appears to be the best resolution to the issue, and lack of that study prior to marketing does not represent a public health hazard. Modafinil is non-genotoxic, and was negative in a 2 year rat bioassay, indicating a low potential for carcinogenicity. The 18 month mouse study, even though conducted at doses that were too low, does provide some additional reassurance.

The patient population for whom modafinil is indicated includes women of child-bearing potential. With respect to the reproductive toxicity studies submitted, modafinil appears to have a very low potential for toxic effects on reproduction and on the developing fetus. However, it has been shown to have some effects, and the extent of those effects has not been fully explored because of the use of inadequate doses in the fertility and teratology studies. Additionally, those studies were non-GLP, further diminishing our ability to rely on them as being definitive. If it were not for the fact that a threshold dose for teratogenicity has been identified in the rat, I would say that we cannot rely on them at all and that this NDA would not be approvable. Because we do have that information, together with information from the one acceptable reproduction study which indicates that there are no effects on behavior and learning, there is some assurance that reproductive effects of this drug are minimal. However, the fertility (segment I) and teratology (segment II) studies must be repeated under GLP regulations and using doses high enough to cause some maternal toxicity. The Precautions section of labeling should include a statement which indicates that effects on fertility and the fetus have not been fully evaluated.

RECOMMENDATIONS

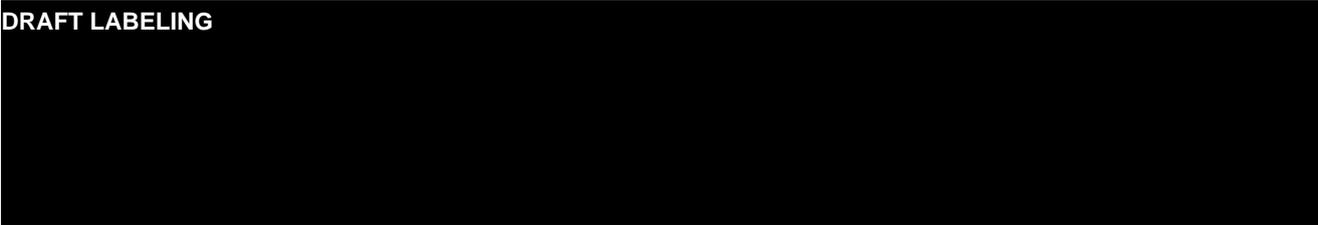
This NDA may be considered approvable

Following is recommended labeling.

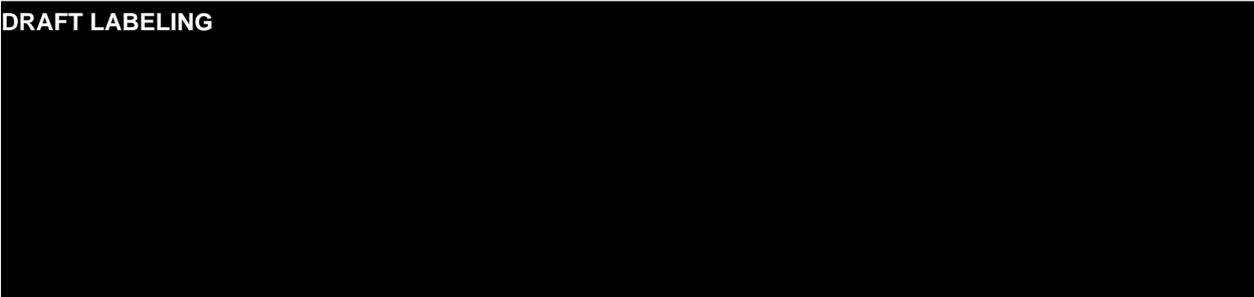
RECOMMENDED LABELING

CLINICAL PHARMACOLOGY

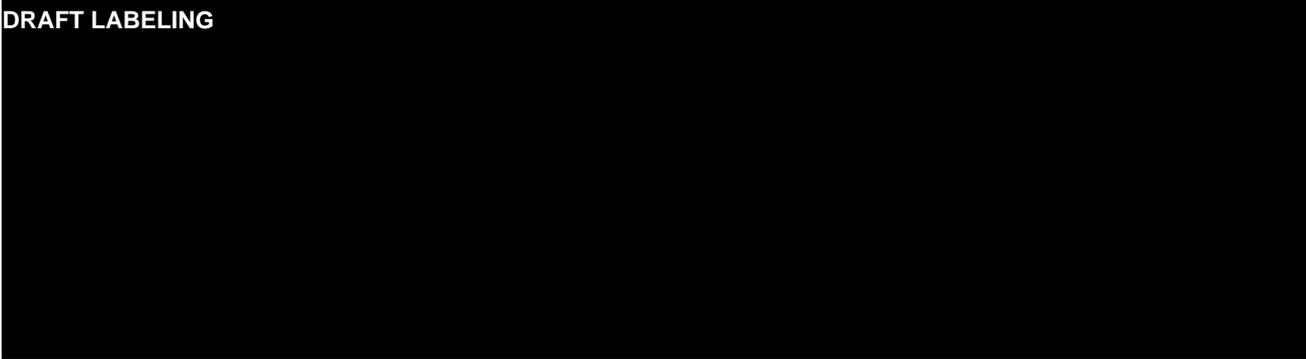
DRAFT LABELING



DRAFT LABELING



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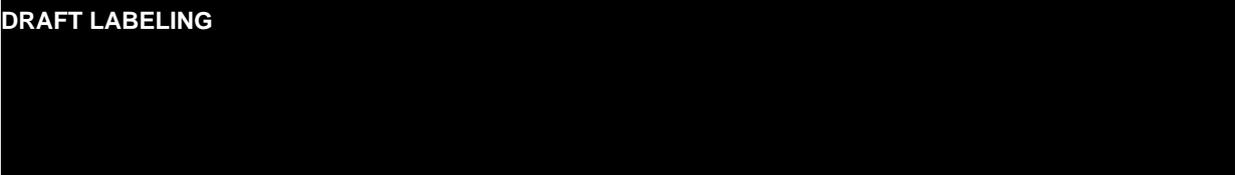


PRECAUTIONS

General:

Reproductive Toxicology

DRAFT LABELING



and PREGNANCY).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

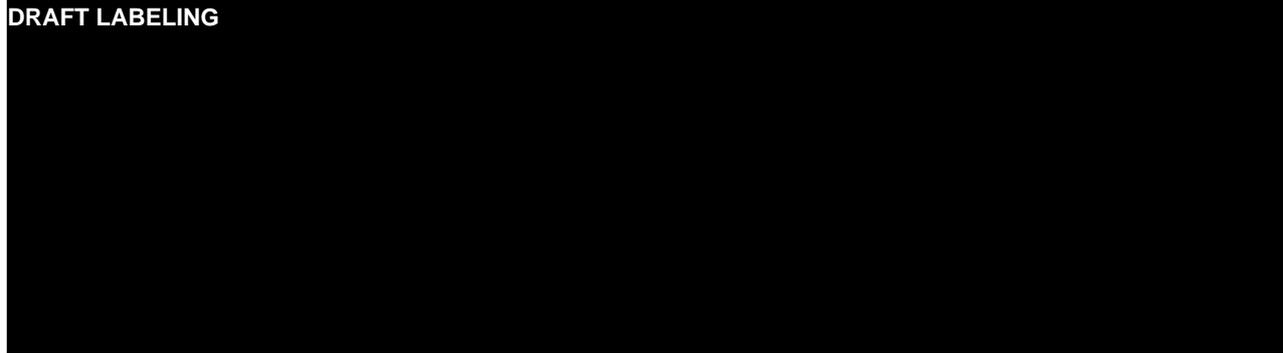
Carcinogenesis:

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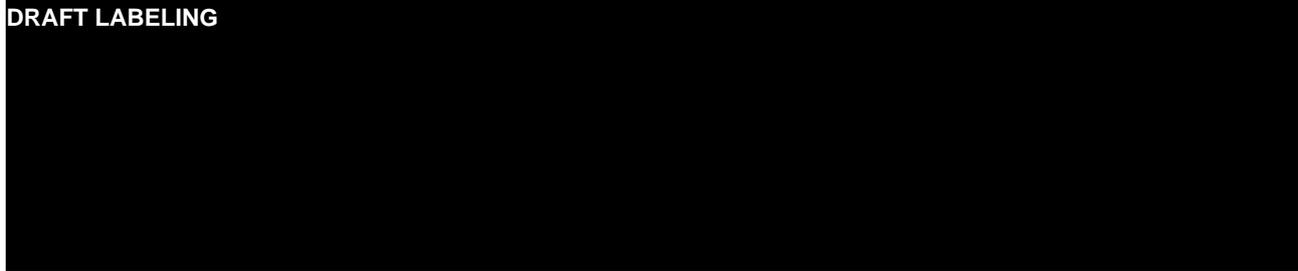
Mutagenesis:

DRAFT LABELING

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Impairment of Fertility:

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PREGNANCY

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DRUG ABUSE AND DEPENDENCE

Preclinical

DRAFT LABELING

OVERDOSAGE

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/S/

Glenna G. Fitzgerald, Ph.D.

Attachments

NDA 20-717

c.c. Div. File

Leber, Katz, Rappoport, Atrakchi, Fisher, Fitzgerald, Malandruccho

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APPEARS THIS WAY ON ORIGINAL

NDA# 20-717
Original Pharmacology Review

NDA# 20-717
Drug: Modafinil (Provigil)
Sponsor: Cephalon, Inc.
West Chester, PA 19380-4245
Indication: Narcolepsy
Category: Unknown mechanism of action, has agonistic effects on central α
adrenergic and dopamine receptors.
Sub Date: Dec 27 1996
Rec Date: Dec 30 1996
Rev Date: Mar 31st 1997
Reviewer: Aisar H. Atrakchi, Ph.D. /S/ [REDACTED]
Team Leader: Glenna Fitzgerald, Ph.D. /S/ [REDACTED]
Related INDNDA(s): [REDACTED]

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EXECUTIVE SUMMARY:

PHARMACOLOGY:

- ◆ The pharmacology of modafinil has been studied in a number of species: mouse, rat, g.pig, rabbit, dog, monkey, and cat.
 - ◆ The exact site of action of modafinil responsible for wakefulness is unknown. Its awakening properties are attributed to multiple sites to include 5HT, DA, and GABA systems, with the requirement of an intact $\alpha 1$ adrenergic system. Modafinil's effects are pharmacologically distinct from amphetamine, methylphenidate, and other psychomotor stimulants such as caffeine. It does not affect the release or uptake of catecholamines nor does it interact with adenosine receptors or blocks phosphodiesterase activity.
 - ◆ In cocaine-trained monkeys, modafinil was a reinforcer for self-administration, in the rat, modafinil did not induce i.v. self-administration or re-inforcement of response, whereas, cocaine did.
 - ◆ Modafinil did not interact with other drugs such as antidepressants (clomipramine, chlorpromazine), antipsychotics (haloperidol), others e.g. prazosin, or warfarin.
 - ◆ Findings from both receptor binding studies and functional studies, indicate that modafinil is unlikely to act via a direct binding to adrenergic receptors since it binds either weakly (IC_{50} 328uM) or not at all (K_i >1000uM) nor does it act indirectly on the release of catecholamines via in vivo models.
 - ◆ Modafinil has limited or no peripheral effects on the CVS, respiratory, or immunologic systems, GI movement, biliary, or pancreatic secretions, urine flow or blood coagulation.
 - ◆ The minimum effective dose range of modafinil's various pharmacology effects are as follows:

Mouse	4->256*mg/kg i.p.
Rat	1 (BID for 5d)-128mg/kg i.p., and 512*mg/kg p.o.
Dog	5&10**mg/kg i.v.
Monkey	6-22.5mg/kg p.o.
Cat	5mg/kg p.o.
- * the high dose represents stereotype behavior.
 ** in genetic dobermans and narcoleptic English bulldog respectively.
 The above effective doses were for hyperactivity, locomotion, stereotypy, incr wakefulness, decr in barbital sleeping time, Porsolt's test, avoidance auditory, and other. Increased wakefulness in the rat, dog, and cat occurred at 30mg/kg i.p., 5mg/kg i.v., and 5mg/kg p.o. respectively.
- ◆ The sulfone metabolite of modafinil was found to be devoid of pharmacological activity in the mouse between 8-512mg/kg i.p. doses. Similarly, the acid metabolite showed no activity in the mouse at 8-512mg/kg and rat at 4-256mg/kg.

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TOXICOLOGY:

- ◆ LD₅₀ values for acute tox studies were as follows:

LD ₅₀ (mg/kg)	Species/Route	Multiples of Human Dose*
1600	rat/p.o.	187
1250	mouse/p.o.	239
1400	rat/i.p.	118
790	mouse/i.p.	209

* 400mg/d or 6.7mg/kg/d for a 60kg person.

MLD (minimum lethal dose) in the dog was 300mg/kg p.o. which is 45x the max human dose of 400mg/d.

- ◆ The following dietary subchronic tox studies were done:

Mouse	13wk (2 studies)	Dose range tested (mg/kg) 25-180
Rat	4wk, 12wk, 13wk, and 26wk	Dose range tested (mg/kg) 20-400
Dog	12wk	Dose range tested (mg/kg)

- ◆ The following dietary chronic tox studies were done:

Mouse	78wk car study	Doses (mg/kg) 6, 30, 60
Rat	2yr car study with 52wk interim sacrifice	Doses (mg/kg) 6, 30, 60
Dog	52wk	Doses (mg/kg) 10, 20, 40

The NOEL were:

Rat	100mg/kg in 4wk	20mg/kg in 26wk	6mg/kg in 52wk and carcinog. studies
Mouse	6mg/kg in the carcinogenicity study,		
Dog	<20mg/kg		

The 6mg/kg NOEL dose in the rat and mouse is equivalent to the maximum human dose of 400mg/d on mg/kg basis.

- ◆ The tox findings in the rat and mouse subchronic studies were mild to moderate with no life-threatening toxicity.
- ◆ In the rat subchronic studies, one or more of the following findings were observed: decr in mean wt, food intake, incr in water intake, mild changes in hematology parameters (macrocytic anemia in m&f rats dosed 400mg/kg), incr in liver, spleen, & kidney wt (absol and/or relative wt; sometimes dose-dependently), decr in thymus wt, decr serum creatinine, serum protein incr, incr hepatic CI in rats dosed 100&200mg/kg. [TK data were not done in any of these studies].
- ◆ In the mouse subchronic studies, CD-1 and OF-1 strains were tested; the OF-1 was the one used in the car study. One or more of the following findings were observed: decr in mean wt, wt gain hematology parameters (Hb, bilirub), incr in liver wt, and liver hypertrophy.
- ◆ TK data were not done in the original 3mo mouse study (study conducted prior to car study), attempts were made to measure TK in the recently conducted 13wk tox study in CD-1 mice. However, due to several technical difficulties and values below quantitation limit of the analytical method, the sponsor conducted a 3rd dietary 13wk TK study in CD-1 and OF-1 strains where dosing via gavage was done on d1&90 of study to ensure detection of plasma levels. Plasma levels were measured between 0.5&24hr postdose on days 1, 30, and 90. No difference in TK data between sexes or strains. Mean 1hr plasma levels & exposure decr with time whereas CI incr with time. Highest mean plasma level on d1 at 60mg/kg was 19ug/ml with AUC₀₋₂₄ of

47ug.hr/ml and Cl of 21ml/min/kg, the corresponding values on d30 were 8ug/ml, 15ug.hr/ml, and 65ml/min/kg. These plasma levels and exposure are equal to or several folds lower than the clinical steady state levels following 400mg/d max recommended dose.

- ◆ Dogs treated for 13wk had stereotypy at doses ≥ 20 mg/kg with head movement, agitation, panting, and sometimes hypotension at 100/75mg/kg dose. Mean wt gain was sig decr in all drug grs without an effect on food intake. Irreversible corneal opacity was observed in 1 dog dosed 50mg/kg and 3 out of 6 dogs dosed 100/75mg/kg. Some changes in hematology and clinical chem that reached statistical sig and considered drug related included incr in MCV, platelet, and WBC, incr in cholest., lipids, and ALP. There were no gross or histopath. There were organ wt changes but considered secondary to wt loss. A NOEL could not be determined in this study due to clinical signs and wt loss at 20mg/kg dose.

CARCINOGENICITY:

- ◆ Mouse car study did not reach an MTD, this conclusion was reached by both the reviewer and the CAC-Exec members. The study was negative with regard to tumor findings. Other toxicities were mild and included dose-dependent incr in absol and rel wt of the liver, liver hypertrophy in HD mice, and inhibition of spermatogenesis in MD&HD. TK data could not be measured except on wk4 because they were below detection limit of the analytical method; at wk4 values ranged between 0.023-0.102ug/ml in 6mg/kg to 0.205-0.402ug/ml in 60mg/kg dose gr.
- ◆ It is the opinion of the reviewer that similar to the mouse car study, an MTD was not reached in the rat study. However, the CAC-Exec members considered the rat car study adequate and that HD reached an MTD based on incr in severity of chronic progressive nephrosis (CPN) in male rats that led to incr in mortality in this gr. Mean wt although decr in HDm during wk80 and mean wt gain decr in HDm&f during wks 52-80, the final mean wt and wt gain were comparable to the controls. The study was negative with regard to tumor findings. Other toxicities in addition to the above, was dose-dependent incr in periarteritis nodosa in testes but this is reported to occur parallel to CPN in rats. TK data were determined for the parent and acid metabolite (main metabolite in humans). As in the mouse car study, the analytical method was not validated, animals were non-fasted, and contamination of cont samples with the drug sub. Modafinil plasma levels ranged between 0-0.035ug/ml in 6mg/kg, 0.24-0.171ug/ml in 30mg/kg, and 0.044-0.180ug/ml in 60mg/kg dose gr. The acid metabolite conc ranged between 0-0.035ug/ml in 6mg/kg, 0.032-0.142ug/ml in 30mg/kg, and 0.059-0.296ug/ml in 60mg/kg dose gr. Plasma $t_{1/2}$ was 1-3hr compared with the long half life in humans of 10-12hr. Plasma levels incr non-linearly with dose.
- ◆ The CAC-Exec recommended that if the sponsor considers the mouse car study is adequate, they may come in and present their case to the CAC. Also they recommended an alternative in vivo assay to be conducted to replace the invalid mouse car study. The sponsor is to submit a protocol and present it to the CAC with justification for using that particular assay.

PHARMACOKINETICS:

- ◆ The PK and/or metabolism of modafinil were investigated in the rat, mouse, dog, and rabbits following single and/or repeate dosing.
- ◆ Concentration-response relationship of modafinil and its acid metabolite was tested using spontaneous motor activity as the end point. Modafinil was injected i.p. at 8, 16, 32, 64, or 128mg/kg to rats. The data showed no correlation between motor activity and mean plasma levels of modafinil but a positive correlation was observed between the individual plasma values and motor activity.

Plasma conc of the acid were generally higher than those of MDF:

Time	Dose (mg/kg)				
	8	16	32	64	128
0	0.8±0.34 (1±0.5)	1.1±0.5 (1.8±0.8)	2.3±0.8 (4±1.4)	6.4±3.6 (7±1.5)	9±3 (13±4.5)
0.5	0.11±0.2 (0.2±0.2)	0.2±0.2 (0.5±0.2)	2±2.6 (3±2)	2±1.3 (4±2.6)	11±4.6 (13±4.6)

Values are means±s.d. in ug/ml; () are the acid conc.

- ◆ In another concentration-response study, modafinil conc was checked against EEG in rats injected i.p. at 128mg/kg for 14days. Values are means±s.d. in ug/ml; () are the range of values. These are 2hr values:

Day	MDF	MDF-acid	MDF-sulfone
1	28.4±27 (0.2-54.5)	10±9 (0.07-18)	8±8 (0-16)
7	13±8 (4-20)	12±5 (8-18)	6±3 (3-9)
14	8±10 (1-20)	5±4.6 (2-10)	3±5.5 (ND-10)

Values measured at 4hr postdose were similar to the above (2hr).

It is clear from these results that with time, conc of MDF and its metabolites decr when given the same dose. There was a great deal of interindividual variation in the data.

- ◆ Modafinil is well absorbed after single and repeated dosing in mouse, rat, and dog. Absolute oral bioavailability was calculated at 80->85% in the dog and rat. Plasma levels correlated somewhat with doses and the kinetics were dose-independent.
- ◆ Elimination half lives were short in rodents (1-3 hr) and dog (2-5 hr) compared with human $t_{1/2}$ of 10-15hr. There were minimal sex differences in PK parameters.
- ◆ Modafinil in the rat, mouse, dog, and humans induces its own metabolism through induction of hepatic drug metabolizing enzymes. This was evident by increase in liver weight, decrease in drug plasma levels after repeated dosing, increased rate of antipyrine metabolism, and in vitro studies.
- ◆ Modafinil is distributed to various tissues such as the liver, kidneys, and endocrines; brain levels were low but constant and homogeneous throughout the brain regions.
- ◆ Modafinil is metabolized mainly to 2 major metabolites: the acid and sulfone. In humans, 6 metabolites have been detected (not all identified) with the acid and sulfone being the main ones.
- ◆ Modafinil is excreted mainly via the urine and some in feces. The drug enters the enterohepatic circulation as it is secreted by the bile in the rat (18-32%).

- ◆ Studies of the stereoisomers indicate small differences in disposition or elimination compared with the racemate (modafinil). The acid and sulfone metabolites were inactive pharmacologically and some differences in intensity of responses were noted between the isomers and the racemate with the d-form being more readily and completely absorbed than the l-form.
- ◆ Due to high auto-induction of metabolism, detection and measurement of plasma levels and other PK parameters of the parent and metabolites was difficult and many times impossible after repeated dosing. This was evident in the inability to measure plasma levels in the 13wk mouse toxicology studies and rodent life-time bioassays.

REPRODUCTIVE AND DEVELOPMENTAL STUDIES:

- ◆ Modafinil effect on reproductive and/or developmental parameters was tested in the following studies:
 1. Seg I in rats/doses: 20, 50, 100mg/kg/Non-GLP
 2. Seg II in rats/doses: 50, 100, 200mg/kg/d/Non-GLP
 3. Seg II in rabbits/doses: 25, 50, and 100mg/kg/Non-GLP
 4. Seg III in rats/doses: 20, 50, 100mg/kg/GLP
 5. Seg III in rats/doses: 50, 100, 200mg/kg/GLP

The NOEL values are as follows:

Study	End-point	NOEL (mg/kg)
Seg I rat	fertility	100
Seg II rat	maternal tox	200
	teratogenicity	200
	embryotox	200
Seg II rabbit	maternal tox	50
	teratogenicity	100
	embryotox	100
Seg III rat	maternal tox	100
	teratogenicity	100
	embryotox	20
Seg III rat	maternal tox	100
	teratogenicity	200
	embryotox	200

Modafinil administered orally to rats upto 200mg/kg and to rabbits upto 100mg/kg was not teratogenic (the 200mg/kg dose is 30x the max anticipated human dose of 400mg/d on mg/kg basis). Fertility in male and female rats was not affected upto 100mg/kg. Embryotox seen as incr resorptions, occurred at 100mg/kg in F0&F1 rats. In absence of maternal toxicity, modafinil in a Seg II rat study incr total no. of resorptions in females dosed 200mg/kg, in addition, there was an incr in litter hydronephrosis and incomp ossification in fetuses from these females. These embryo-fetal toxicities may not be of real biological significance because the number of resorptions per female was not affected and the visceral and skeletal effects were relatively small. The NOEL for embryotoxicity in this study is therefore, 200mg/kg. Rabbits dosed modafinil during organogenesis period, showed a small decr in mean wt gain and food intake at 100mg/kg. The NOEL in rabbits was 50mg/kg for maternal tox and 100mg/kg for embryotox and teratogenicity. In a pre- and post-natal Seg III rat study, modafinil was dosed during pregnancy and lactation. There was a dose-dependent incr in RI but stated by the sponsor to be within historical data for this rat strain. Though dose-

independent, number of live fetuses per female was decr in all 3 drug grs and the stillborn rate and number of stillborns were incr in females dosed 50&100mg/kg. The only effect on growth was a delay in startle response in the 50&100mg/kg dosed groups. The maternal NOEL is 100mg/kg whereas, that for embryotoxicity is 20mg/kg. In a more recent Seg III study in rats, modafinil was not teratogenic upto 200mg/kg but caused a 40% decr in wt gain in females in this gr during gestation period 7-10; no effect thereafter. This decr however, affected the cummulative wt during gestation periods 7-20&0-20. Mean wt was slightly but sig decr during lactation period. Accompanying the decr in wt was a 7-20% decr in food intake in the 100&200mg/kg dosed grs during gestation periods 7-10&7-20. In contrast to the previous Seg III study where the NOEL for embryotoxicity was 20mg/kg, in this repeate study, modafinil was not embryotoxic upto 200mg/kg; the maternal NOEL was 100mg/kg similar to that in the previous study.

GENETIC TOXICOLOGY:

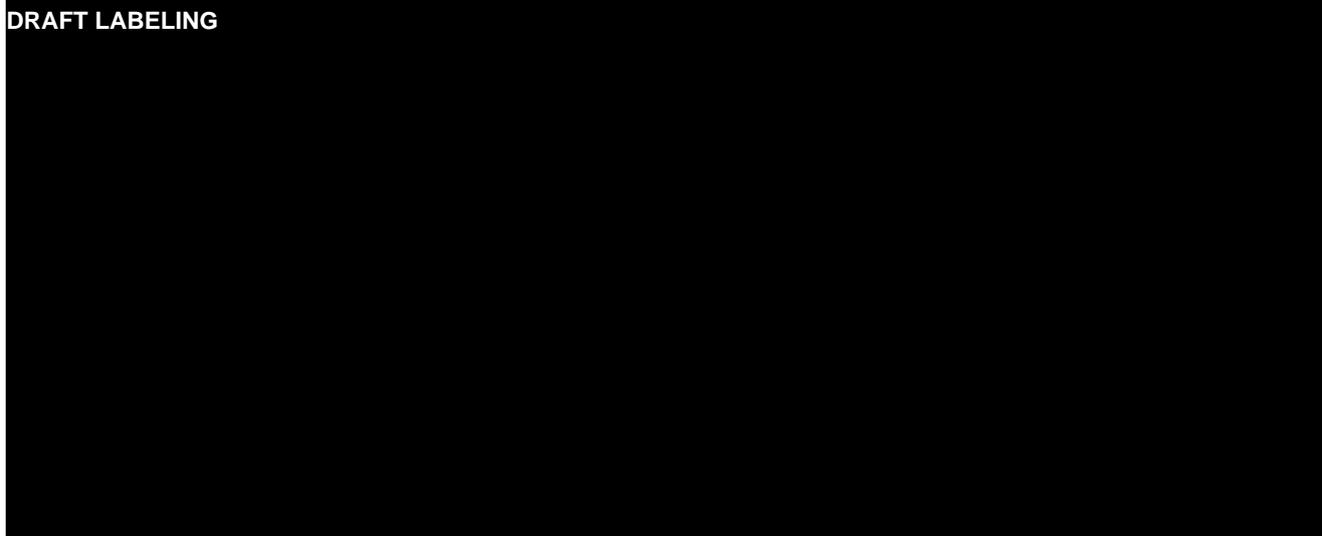
- ◆ Modafinil was not mutagenic in the assays evaluated. The following tests were conducted: Ames test, human lymphocyte chromosome aberration, chinese hamster V79 lung fibroblasts gene mutation, and in vivo chinese hamster bone marrow chromosome aberration assay.

APPEARS THIS WAY ON ORIGINAL

LABELING:

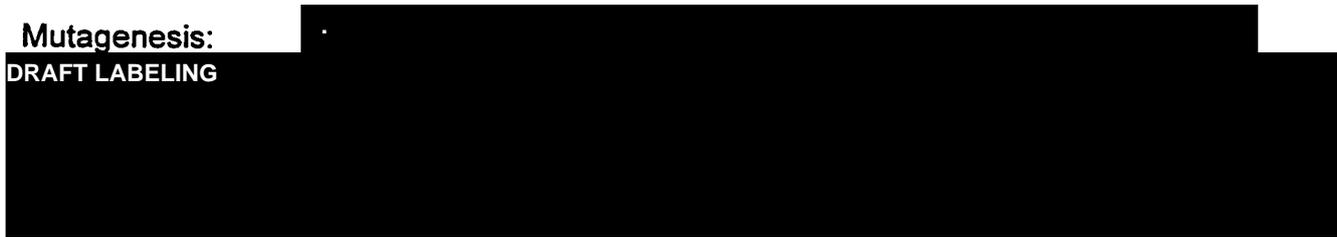
Carcinogenesis, Mutagenesis, Impairment of Fertility:

DRAFT LABELING



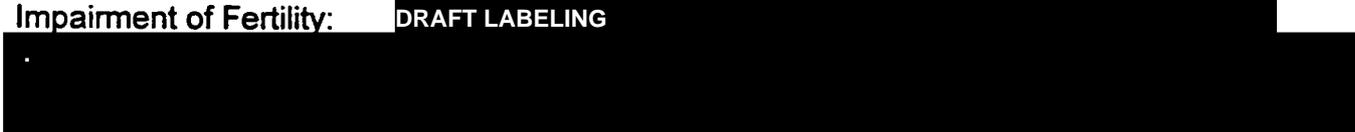
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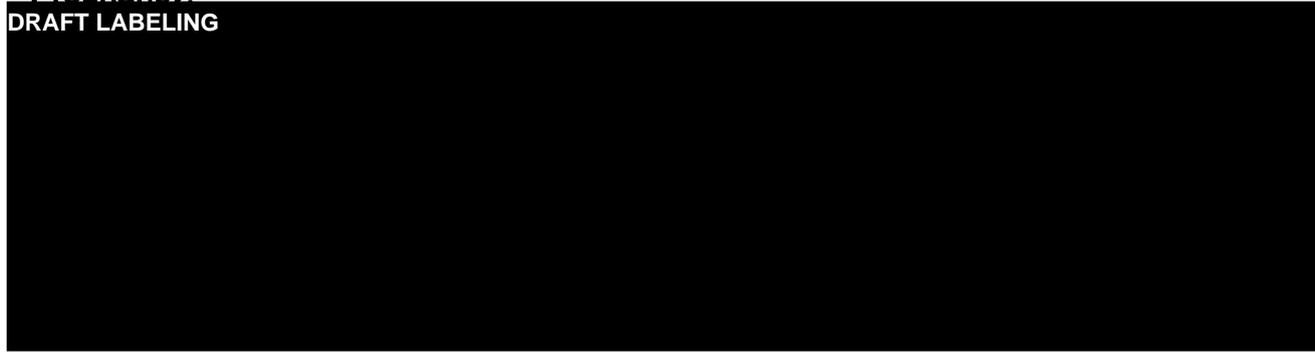
Impairment of Fertility:

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Pregnancy:

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Pharmacology**Mechanism of Action:**

Large number of in vitro and in vivo studies have been done to investigate the mechanism/site of action of modafinil. The results from all studies indicated that there is no specific mechanism of action for modafinil. Its awakening properties can be attributed to multiple sites such as 5HT, DA, and GABA systems, with the requirement of an intact $\alpha 1$ adrenergic system. Unlike other drugs useful in narcolepsy such as amphetamine or methylphenidate, modafinil at therapeutic doses does not affect release or re-uptake of catecholamines and has no effect on locomotor activity or stereotypy. These findings indicate that modafinil has a unique mechanism of action regarding wakefulness that is distinct from other drugs used in narcolepsy. Modafinil has limited or no peripheral effect on the CVS, respiratory, or immunologic systems, GI movement, biliary, or pancreatic secretions, urine flow or blood coagulation. The minimum effective dose range of modafinil's various pharmacology effects are as follows:

Mouse	4->256*mg/kg i.p.
Rat	1 (BID for 5d)-128mg/kg i.p., and 512*mg/kg p.o.
Dog	5&10**mg/kg i.v.
Monkey	6-22.5mg/kg p.o.
Cat	5mg/kg p.o.

* the high dose represents stereotype behavior.

** in genetic dobermans and narcoleptic English bulldog respectively.

Increased wakefulness in the rat, dog, and cat occurred at 30mg/kg i.p., 5mg/kg i.v., and 5mg/kg p.o. respectively. The above effective doses were for hyperactivity, locomotion, stereotypy, incr wakefulness, decr in barbital sleeping time, Porsolt's test, avoidance auditory, and other.

The following discussion represents selected reports from the large number of studies conducted (some of these studies are published articles). In vivo differential pulse voltametry was used to study the extracellular catechol level in the caudate nucleus of anesthetized implanted mice. Modafinil (16-256mg/kg) did not modify the catechol oxidation peak height, d-amphetamine decr it at 2-4mg/kg whereas, 8mg/kg had no effect, and, methylphenidate incr the peak at 32&64mg/kg. It was concluded that modafinil unlike d-amphetamine and methylphenidate, did not change synaptic catechol conc or turnover in the nigro-striatal neurons ending in the caudate nucleus. From in vitro studies, modafinil was not a ligand for DA uptake. An in vivo study was done to assess if modafinil has any DA activity. Unilateral lesion of the nigrostriatal pathway was done with 6-OHDA in SD rats and the ability of modafinil to induce contra- or ipsilateral turning was compared with cocaine (a DA uptake inhibitor). Rats were pretested with amphetamine and those with >50 ipsilateral rotations were selected. The results showed that modafinil upto 300mg/kg did not induce ipsi- or contralateral rotations in the 6OHDA-lesioned rats in contrast to 20mg/kg cocaine that produced a sig incr in number of ipsilateral rotations. Cortical glutamine and glutamate levels were measured in rats using instrumental (water tank) and pharmacological methods (modafinil 128mg/kg, i.p.) to induce paradoxical sleep deprivation (PSD). Two types of control rats were used in the instrumental method, one remained in isolated cages, and in order to assess the effect on stress, the 2nd gr was placed on a 12cm platforms that allowed PS (REM). Rats were killed during wake and sleep stages and brain levels measured by [redacted]. Rats exposed to instrumental sleep deprivation showed a sig incr in glutamine and glutamate levels ($P < 0.05/0.001$) which was still observed in the sleep-rebound period. GABA level was not affected but did incr in the rebound period. In contrast, modafinil-induced PSD did not affect brain AA levels. The investigators contributed this difference to the shorter arousal effect of modafinil of 4hr vs. upto 24hr with the water tank. This was confirmed in a separate exp where rats were killed after only 5hr of instrumental PSD and the levels of these AA were not affected. In vivo GABA/DA interactions were studied in anesthetized rats through microdialysis in the nucleus accumbens. Modafinil dose-dependently (100&300mg/kg, s.c.) incr DA and decr GABA release; 30mg/kg modafinil was ineffective. This incr in DA by modafinil was reversed by local infusion of GABA_B antagonist (phaclofen), GABA_A agonist (muscimol), and GABA reuptake inhibitor (SKF589976A), but the release was incr by GABA_B agonist (baclofen). This finding suggested that modafinil-induced release of DA in the

nucleus accumbens is mediated by its ability to decrease local GABAergic transmission. The latter causes decrease in GABA_A receptor signaling on the DA terminals. In an in vitro study, modafinil was a weak inhibitor of DA uptake compared with either nomifensine or cocaine and it did not induce DA release in the same manner as d-amphetamine. The affinity of modafinil to the DA transporter was 2 μM or 30x lower than that of nomifensine and modafinil was 100x less potent than nomifensine in increasing spontaneous and electrically-evoked release of ³H-DA from superfused rat striatal slices. The inhibitory effect of modafinil, its enantiomers, and metabolites (the acid and the sulfone) on uptake of monoamines by striatal (DA, 5HT) and cortical (DA, 5HT, NA) rat synaptosomes, was studied. The positive controls in this study were nomifensine, fluoxetine, and desipramine. The K_i for modafinil on uptake of DA (except in the striatal preps) ranged between 10⁻⁶ to 10⁻³M whereas that for nomifensine, fluoxetine, and desipramine ranged between 10⁻⁶ to 10⁻⁸M. The results showed that modafinil, its enantiomers, and metabolites were not strong inhibitors of monoamine uptake in striatum or cortical synaptosomes compared to the positive controls. To determine the potential of modafinil to interact with nitric oxide synthetase (NOS), assays were done to measure the activity of constitutive and inducible NOS in +/- of modafinil. Results showed that modafinil at 10 μM, had no activity (≤4%) against constitutive or induced NOS indicating that the wakefulness properties of modafinil are not mediated via inhibition of NOS activity.

Receptor Binding:

In vitro: Radiolabel binding of ³H-MDF was studied in cerebral membranes of the mouse, rat, dog, and rabbit. ³H-MDF (8 nM) did not bind to any brain structure of any of these species.

In vivo: mice were injected i.p. cold MDF (256mg/kg) or saline, 30min prior to i.v. injection of 12.5 μCi of ³H-MDF and animals sacrificed 10-90min postdose. Radioactivity was examined in pons, striatum, and cortex. MDF did not show any specific binding in any brain structure tested.

Displacement of ³H-prazosin/In vitro: cold prazosin strongly displaced ³H-prazosin with IC₅₀ of 25.6nM whereas, MDF showed low affinity with IC₅₀ of 328 μM.

Ex vivo: MDF administered orally to mice at 64mg/kg 2x per day for 4 or 18 days. On day 5 or 19 MDF was administered 1hr prior to sacrifice. Cortical membranes were prepared and radioactivity measured. No significant changes were noted in B_{max} or K_d of ³H-prazosin at 4 days however, after 18 days and on the morning of day 19, MDF caused a significant increase in B_{max} and K_d of ³H-prazosin 1 hr postdose. NOVAScreen was done recently (1994) and modafinil upto 0.1mM did not bind any of the receptors nor did it bind to any receptors to second messengers upto 1mM (phorbol ester, adenylate cyclase, and inositol triphosphate). Modafinil showed no binding inhibition except to DA uptake with 100% inhibition, IC₅₀ was 3.2 μM with K_i of 2 μM. This binding was selective to DA with no affinity to adrenergic or 5HT transporters upto 100x higher conc than the IC₅₀ for DA uptake. Modafinil was also shown not to bind to H3 or melatonin receptors in the rat brain and chicken brain membranes respectively.

Effects Related to Proposed Indication:

The effects of modafinil were compared to methamphetamine on parameters of arousal and locomotor activity (LMA) in rats. Modafinil was injected i.p. at 30, 100, 300mg/kg and methamphetamine at 0.5&1mg/kg. Modafinil enhanced wakefulness without affecting LMA and in contrast to methamph, it did not induce sharp and intense drive for the compensatory NREM once the wake-promoting effect was subsided. Modafinil-induced wakefulness was longer and un-interrupted and the REM duration was reduced compared with the effects of methamphetamine on these parameters. This study showed that the effects of modafinil on arousal and LMA are different from those of methamphetamine. A study was done to verify modafinil's induction of wakefulness without an increase in compensatory NREM sleep a finding, that is in contrast to that of methamphetamine. Rats were deprived of sleep for 6hr and parameters of arousal were measured after 100&300mg/kg modafinil. The results showed that modafinil prolonged wakefulness in sleep-deprived rats without increasing depth of NREM sleep or the desire to recover lost NREM. At 300mg/kg, modafinil reduced the amount of lost NREM & REM recovered after the period of extended wakefulness. Therefore, it was concluded that modafinil reduced preexisting sleep debt caused by forced wakefulness and accumulation of additional REM sleep debt incurred during this period. In anesthetized rats, sleep/wake cycles were studied after i.p. inj of modafinil at 32, 64, 128, or 250mg/kg.

Modafinil caused dose-dependent incr in wakefulness, with a decr in SWS1, SWS2, and REM for 2hr post inj; the duration of these parameters was also dose-dependent (4hr at 128mg/kg and 8hr at 250mg/kg). Effect of modafinil and d-amphetamine on recovery of paradoxical sleep (PS) was tested in rats implanted with electrodes. Modafinil (64&128mg/kg, i.p.) caused a dose-dependent incr in wakefulness and sleep reappeared with SWS recovery on day of inj without recovery of lost PS. Comparable results were seen at 128mg/kg modafinil and 2.5mg/kg d-amphetamine however, the latter led to subsequent recovery of both lost SWS & PS.

The English bulldog model of hypersomnolence was used to examine the effect of modafinil (10mg/kg i.v.) on wakefulness and sleep. These dogs have disordered respiration and episodes of oxygen desaturation also, they have abnormal airway anatomy. The following parameters were measured: total sleep time (TST, % of total sleep time divided by the total study time), sleep latency (total minutes till onset of NREM), and sleep disordered breathing index (SDBI). Modafinil caused marked wakefulness demonstrated by sig decr in TST (8 ± 7 vs. $51\pm 15\%$ in vehicle cont; $p\leq 0.005$) and incr in sleep latency (347 ± 105 min vs. 71 ± 40 min in vehicle cont; $p\leq 0.005$); no effect on SDBI. Another canine model for sleep disorders is the narcoleptic dobermans. The effects of both modafinil and d-amphetamine on cataplexy and excessive sleepiness were compared using dobermans implanted with EEG, EOG, and EMG electrodes. Other parameters assessed included body temp, LMA, and CVS (HR&BP). Canine cataplexy is exacerbated by $\alpha 1$ adrenergic antagonist and reduced by $\alpha 1$ adrenergic agonists. Normal dogs served as the vehicle cont and received saline or DMSO i.v., the narcoleptic dobermans received modafinil at 0.125, 0.5, 2, and 8mg/kg i.v., or d-amphetamine at 2.5, 10, 40, 160ug/kg; doses of 5&10mg/kg modafinil and 100&200ug/kg d-amphetamine were tested for wakefulness. Modafinil at 10mg/kg and d-amphetamine at 200ug/kg showed equal efficacy in incr wakefulness and decr deep sleep in both the normal and narcoleptic dogs. However, unlike d-amphetamine, modafinil sig reduced REM in both normal and narcoleptic dogs and reduced light sleep only in the normal dogs. d-amphetamine but not modafinil, completely suppressed cataplexy in all dogs for upto 1hr and decr it for upto 6hr ($p<0.001$). In contrast, modafinil had no effect on suppression and/or decr in cataplexy at the highest dose tested (10mg/kg). Modafinil had no effect LMA, HR, or rectal temp but it caused a small but statistically sig decr in BP. It is known that the $\alpha 1$ agonists are potent anticataplectic cpds in the dobermans model of narcolepsy and possess acute hypertensive effects. Absence of these effects from modafinil suggested that it does not have a direct or indirect $\alpha 1$ agonistic properties.

In summary, the large number of in vivo and in vitro studies showed no specific biochemical mechanism of action of modafinil. Modafinil-induced wakefulness involves mechanism(s) other than direct agonist or antagonistic effect on catecholamine receptor sites. Its mechanism of action could involve multiple sites such as 5HT, DA, or GABA, all with the requirement of an intact $\alpha 1$ adrenergic system. Radioreceptor binding and uptake assays failed to reveal any specific binding of modafinil to the large number of receptor sites assayed. Radiolabelled modafinil failed to bind to brain tissue from the mouse, rat, rabbit, and dog thus indicating absence of unique binding site in the brain. It is noted that the mechanism of modafinil is distinct from that of amphetamine or methylphenidate and is independent on newly synthesized catecholamines. Also, there is no evidence that modafinil affects the release of NA nor does it affect postsynaptic response. Unlike amphetamine, modafinil has no effect on cataplexy or LMA.

Other Effects:

Neuroprotection:

- At 100mg/kg/d i.p., modafinil protected against MPTP-induced damage to nigrostriatal DA neurones.
- counteracted dose-dependently (10, 30, 100mg/kg, i.p.), the decr in tyrosine hydroxylase immunoreactive cell bodies and nerve terminals and DA stores in the rat nigrostriatal DA pathway.
- counteracted dose-dependently (30&100mg/kg, i.p.), the ischemic striatal injury induced by microinjection of endothelin-1 into the neostriatum. The mechanism did not seem to involve incr in striatal blood flow but rather, a decr in anaerobic metabolism (lactate level).

GI Effects:

No effect on intestinal peristalsis in anesthetized dog.

Immunology:

Slight stimulation of humoral immunity, not cellular immunity in mice.

Activity of Metabolites:

The behavioral activity of the sulfone was examined in mice with no changes upto 32mg/kg i.p. Higher doses ≥ 64 mg/kg i.p. caused abdominal stretching, vocalization, dyspnea, and sedation. In rats, mydriasis and decr reactivity to touch were seen at ≥ 4 mg/kg i.p. and decr muscle tone observed at ≥ 64 mg/kg. Modafinil sulfone at 512mg/kg i.p. slightly incr reserpine-induced hypothermia whereas, modafinil at 256mg/kg decr reserpine-induced hypothermia. The spontaneous locomotor activity in mice was decr by 36&50% after sulfone doses of 128&512mg/kg i.p. On the other hand, the sulfone at 32 or 128mg/kg did not affect the hyperlocomotion induced by 64mg/kg modafinil. Similar to modafinil but at much lower potency, the sulfone incr locomotor activity in mice habituated to their enclosure by 402% at 512mg/kg (vs. 897% at 16mg/kg modafinil). It is concluded that modafinil sulfone does not cause behavioral effects. In those cases where an effect was seen, the sulfone was several folds less potent than modafinil in producing an effect such as incr locomotor activity in mice habituated to their enclosure (30 fold less potent). In a separate set of studies, both modafinil sulfone and modafinil acid very weakly inhibited monamine uptake in striatal or cortical synaptosomes when compared to nomifensine, fluoxetine, and desipramine.

Drug-Drug Interactions:

Preclinical studies showed that modafinil did not modify the effects of the following drugs: Antidepressants clomipramine, desipramine, & chlorpromazine; Antipsychotic haloperidol; Anticoagulant warfarin; Antihypertensive prazosin; and others e.g. isoproterenol, Ach, and histamine.

Modafinil modified the effects of the following drugs: decr in the hypertension induced by NA, Epinephrine, amphetamine, DA, tyramine, and angiotensin in anesthetized dog. Modafinil interacted with ethanol through incr in duration of ethanol-induced sleep, aggravated ethanol-induced motor incapacitation, and incr ethanol blood levels. Ethanol caused an incr in blood levels of modafinil and its acid metabolite.

CVS:

Modafinil upto 200mg/kg i.d. had no effect on respiratory rate in dogs. In conscious SHR, modafinil at 200mg/kg p.o. did not affect BP or HR. In anesthetized dog, 100&200mg/kg i.d. modafinil had no effect on arterial blood flow, peripheral resistance, CO, LVP, only mild (7%) decr in HR, and mild to moderate decr in differential BP. A recent study was done to investigate the CVS effects of modafinil co-administered with the antidepressant clomipramine. Antidepressants are usually given to narcoleptics to treat cataplexy. Modafinil doses of 20 or 60mg/kg i.d., were selected to produce max conc comparable to that achieved clinically following a therapeutic as well as an overdose. Clomipramine was administered at 5 doses of 0.1, 0.3, 1, 3, and 10mg/kg with 20min between each escalating dose. Various hemodynamic parameters were evaluated including: MAP, SAP, DAP, CO, dp/dt, contractility (CF), HR, EKG, LVEDP, and LVP. Blood levels of modafinil were determined from samples collected from each dog between 0 and 120min postdose of vehicle or modafinil and additional samples collected 2-3min prior to each dose of the interaction cpd. Results showed clomipramine by itself had no effect on any parameter at 0.1, 0.3, or 1mg/kg doses. At 3 and 10mg/kg, clomipramine caused a small decr in MAP (~25mmHg) and LVP (~30mmHg) these values remained depressed upto 15min postdose. Minimal decr also observed in SAP, DAP, CO, dp/dt, and CF; LVEDP was incr, no effect on EKG parameters. Modafinil alone at 20 and 60mg/kg had no effect on any parameter. When both drugs were co-administered, no attenuation or potentiation was observed and similar changes in the CVS and EKG parameters were observed when

clomipramine (all 5 doses) was administered to dogs pre-treated with either 20 or 60mg/kg modafinil to those observed after clomipramine alone. The mean observed plasma C_{max} level of modafinil

administered alone at 20mg/kg was $4.7 \pm 1 \mu\text{g/ml}$ and in presence of clomipramine was $6.2 \pm 3 \mu\text{g/ml}$. The mean observed plasma level after 60mg/kg was $7 \pm 3 \mu\text{g/ml}$ and in presence of clomipramine it was, $7 \pm 2.4 \mu\text{g/ml}$. These findings indicate that plasma levels incr with dose but the incr was not proportional to dose (non-linear). From the above, it can be seen that 20mg/kg modafinil dose reached the targeted clinical plasma level of 4.8ug/ml but the 60mg/kg dose did not (15.4ug/ml in humans).

PK Studies

Single Dose:

Mice:

This study evaluated dose-response relationship of MDF. NMRI mice (12/sex/dose) were orally administered MDF in gum arabic suspension at 8, 16, 32, 64, or 128mg/kg 30min before placing them in actimeters. Motor activity was measured and plasma levels of MDF and its acid metabolite were determined by [redacted]. Plasma levels corresponded to those measured 1hr after dosing. Plasma levels in males ranged between 1-22 $\mu\text{g/ml}$ and those for females 1-25 $\mu\text{g/ml}$, values for modafinil acid (MA) in males were 0.3-4 $\mu\text{g/ml}$ and 0.2-5 $\mu\text{g/ml}$ in females. Plasma levels of MDF and its acid metabolite increased linearly with dose, plasma levels of MA however, were much less than those of MDF. No significant sex differences were noted in plasma levels but female plasma levels in general, were higher than those of males. A linear relationship was noted between plasma concentration and response (motor activity).

Rat:

Single 50mg/kg MDF dose was orally administered to 3 SD rats. Animals were killed at given intervals and blood sampled for drug measurement. From 1hr and until 5.5hr postdose, MA concentration was higher than the parent drug, a kinetic profile different from that in the mouse. $t_{1/2}$ was 1.6hr, plasma level ranged between 5 $\mu\text{g/ml}$ at 0.5hr and 0.2 $\mu\text{g/ml}$ at 2hr, and MA concentration range was 2.5 $\mu\text{g/ml}$ at 0.7hr and 0.8 $\mu\text{g/ml}$ at 2hr.

Sprague-Dawley male rats (3/time point) were injected i.v. 5mg/kg modafinil. The AUC_{0-4hr} was 2ug.hr/ml and systemic plasma Cl was 3L/hr/kg which is much higher than hepatic blood flow of 1.6L/hr/kg, and the V_d was 2l/kg.

-Comparison of the Kinetics of Modafinil in Male and Female Fischer and SD Rats:

Four to six rats from each sex and strain were injected MDF i.p. at 64 or 256mg/kg. Blood was collected at given times from implanted intraventricular catheters. In either strain except for the sulfone metabolite, females had higher blood concentrations of MDF and MA compared with the males. Also, Fischer rats had higher drug levels than the corresponding Sprague-Dawley rats. At 64mg/kg dose, concentrations of MA were higher than MDF in both sexes of Sprague-Dawley whereas, the values were less or similar in Fischer rats. At 256mg/kg, the opposite was true: the concentration of MA were lower than those of MDF in both strains. The sulfone was determined only in HD and levels were higher in Fischer rats and the levels in males of both strains were higher than those in females. $t_{1/2_{sulf}}$ of the sulfone was longer than that of MDF. Drug $t_{1/2_{sulf}}$ was homogeneous among sexes and strains except in HD female Fischer rats, where $t_{1/2_{sulf}}$ was 14 ± 6 hr compared with 2 ± 0.3 hr in female Sprague-Dawley at this dose indicating the slow absorption of the drug. The plasma profile in Fischer rats seems to be closer to that observed in man. In spite of this similarity to humans, this rat strain was not used in the toxicity or pharmacology studies. $AUC_{0.25-8}$ of modafinil in Fisher rats m:14/f:28ug.hr/ml at 64mg/kg and at 256mg/kg exposure vales were m:261/f:590ug.hr/ml in SD rats: m:6/f:8ug.hr/ml at 64mg/kg and after 256mg/kg m:67/f:218ug.hr/ml.

Dog:

-Linearity of the Kinetics of Modafinil.

Five dogs/dose received single oral doses of MDF in a cachet at: 6.25, 12.5, 25, 50mg/kg in a crossover design. Doses were selected based on toxicity studies. One treatment-free week separated between the doses. Blood was collected at specified times, up to 24hr postdose, and drug levels analyzed using HPLC/UV detector. Results are presented in the Table below.

Time (hr)	Dose (mg/kg)			
	6.25	12.5	25	50
0.25	0.01±0.01	0.33±0.2	0.07±0.07	0.88±0.59
0.5	0.05±0.05	0.64±0.38	0.71±0.46	2.55±1.06
0.75	0.1±0.08	0.89±0.48	1.66±0.57	3.31±1.36
1.0	0.2±0.16	1.71±0.29	2.59±0.32	3.76±1.58
1.5	1.15±0.39	3.2±0.42	4.75±0.96	5.92±1.36
2.0	2.27±0.61	4.04±1.0	5.51±1.45	8.41±1.69
2.5	2.39±0.54	4.45±1.34	5.58±1.79	9.02±1.78
3.0	2.23±0.54	4.42±1.54	5.46±2.01	8.38±1.71
4.0	1.66±0.38	3.72±1.24	4.69±1.93	7.82±1.59
5.5	1.02±0.22	2.61±0.86	3.62±1.3	5.94±1.14
7.0	0.65±0.15	1.78±0.46	2.79±0.81	4.94±1.0
8.5	0.42±0.12	1.19±0.27	2.1±0.55	4.02±1
24.0	0.05±0.01	0.1±0.02	0.22±0.07	0.44±0.14

Values are means±SEM.

Pharmacokinetic parameters:

Dose (mg/kg)	6.25	12.5	25	50
$t_{1/2el}$	1.8±0.32	1.93±0.31	3.3±1.33	3±0.74
$t_{1/2abs}$	0.92±0.25	1.53±0.28	1.47±0.35	1±0.34
AUC _{exp}	14.13±2.53	32.81±7.5	50.35±12.47	87.87±15
C _{max}	2.58±0.62	4.82±1.4	6.3±1.81	10±1.5
T _{max}	2.4±19	2.5±0.22	2.1±0.24	2±0.35

C_{max} is in ug/ml; AUC is in ug.hr/ml; t values are in hr.

The above results indicate that the drug is absorbed slowly with a $t_{1/2abs}$ of 1.3 hr, C_{max} of 6 mg/l and a T_{max} of 2.3hr. A linear relationship was noted between plasma concentration and dose ($r=0.68$) and AUC_{exp}. The V_d is calculated at 2 l/kg, total clearance is approximately 0.6L/hr/kg, and $t_{1/2el}$ 2.5hr (range 1-9hr), irrespective of dose. It is concluded that the kinetics of modafinil is linear in the dog and independent on the dose following a single administration of doses between 6.25 and 50mg/kg.