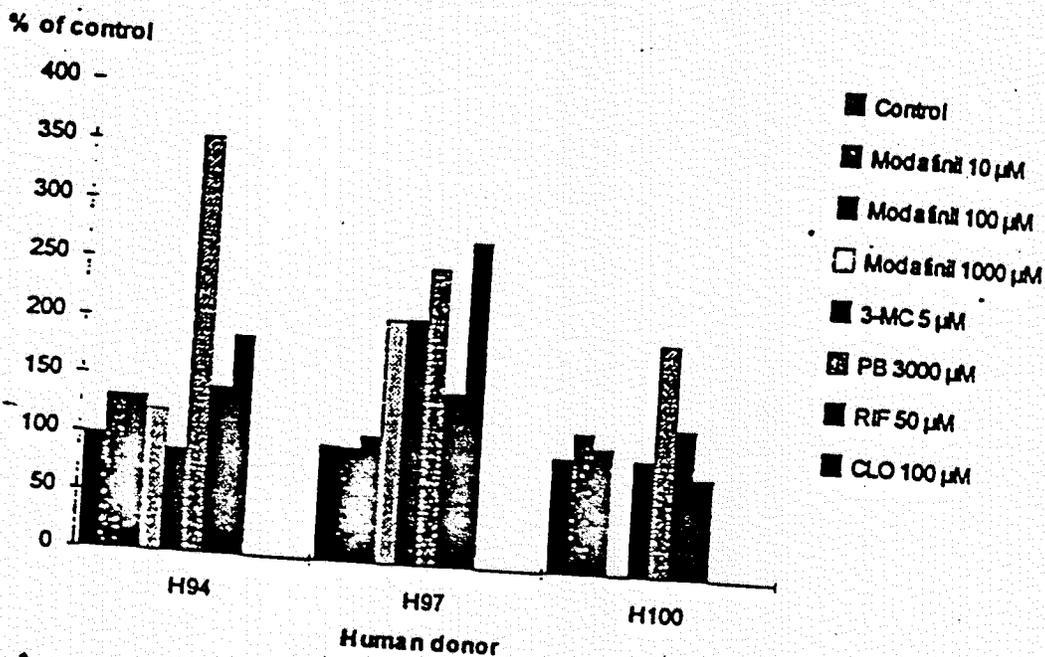


3-MC : 3-methylcholanthrene
PB : phenobarbital
RIF : rifampicin
CLO : clofibrac acid

8.8 - Nifedipine oxidase activity, supported by CYP 3A, in human hepatocyte cultures, after a 72 hour incubation period in the presence of modafinil (Modiodal®) and of reference inducers



3-MC : 3-methylcholanthrene
PB : phenobarbital
RIF : rifampicin
CLO : clofibrac acid

8.9 - Lauric acid hydroxylase activity, supported by CYP 4A, in human hepatocyte cultures, after a 72 hour incubation period in the presence of modafinil (Modiodal®) and of reference inducers

Gélineau's syndrome in a kidney-transplant patient
Observation of a cyclosporine-modafinil interaction

Cyclosporine⁽¹⁾ (CsA), which is widely used as immunosuppressive treatment in organ transplants, is known for its numerous drug interactions [1]. Modafinil⁽²⁾, recently marketed for the treatment of idiopathic hypersomnia and narcolepsy, presents enzyme inducing potential which is capable of reducing the efficacy of certain drugs [2]. The interaction between these two drugs has not yet been shown. We report the first case of Gélineau's syndrome diagnosed in a renal transplant patient.

born in 1954, suffers from chronic renal insufficiency secondary to vesical-ureteral reflux treated with repeated hemodialysis, then by a cadaver-donated kidney transplant in November 1986; the simple after-effects quickly allowed the use of immunosuppressive monotherapy with CsA. The first symptoms of excessive somnolence appeared in January 1995, followed in July by episodes of cataplexy which responded favorably to imipramine (20 then 30 mg/day); the rest of the treatment then associated acebutolol 200 mg, captopril 50 mg, 1 α -vitamin [illeg] 0.5 μ g and CsA 2 x 100 mg/day. The functioning of the graft was stable, with creatinemia 115 μ mol/l, urea 9 mmol/l, residual blood level of CsA t_0 : 110 \pm 10 ng/ml (SYVA specific monoclonal). Polysomnography with test of repeated sleep induction latencies, and haplotyped HLA DR15 and [illeg] confirmed Gélineau's syndrome. Treatment with modafinil 200 mg/day was instituted beginning November, with good clinical response.

On 12 December 1995, a systematic test showed: creatinine 122 μ mol/l, urea 11 mmol/l, no proteinuria, t_0 55 ng/ml. There was no other drug taken, no change in diet which could explain this sudden reduction in t_0 . The doses were increased 25 mg at a time, and it was only with 300 mg/day that relative stabilization of the t_0 was achieved at 80 \pm 10 ng/ml. Kinetics were then tested (Table I).

⁽¹⁾ Sandimmun, Sandoz Laboratories
⁽²⁾ Modiodal

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Table I
Evolution of cyclosporine (CsA) blood levels
as a function of time

Time	CsA (ng/ml)
t0	80
t1	>1000
t2	385
t4	185
t6	101
t8	84

These figures confirm that the reduction in the t_0 - and the necessary increase in posology which followed - is definitely linked to an acceleration of the metabolism and not to reduced bioavailability. This observation serves as a reminder, should such a reminder still be necessary, that any modification in treatment in a transplant recipient must be followed by systematic testing of the kidney function and of the blood level of CsA.

1. Billaud EM, ... [illeg], Clinical evaluation of drug interactions of cyclosporine. *Presse Med* 1988; 17:2293-[illeg].
2. Boivin DB, Montplaisir J, Petit D, Lambert C, Rubin S. Effects of modafinil on symptomatology of human narcolepsy. *Clin Neuropharmacol* 1992; 16: 46-53.

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Bioequivalence study

18. An Open-Label, Randomized, 4x4 Latin Square, Crossover Study to Determine the Relative Bioavailability and Bioequivalence of Three Single Oral (200 mg) Modafinil Tablet Treatments (C1538a/110/BE/UK)

Objectives: This study was designed to first ascertain whether or not the tablet treatments A, B, and C of modafinil were bioequivalent. The second objective of the study was to determine the relative bioavailabilities of the modafinil tablet treatments A, B, and C versus an aqueous suspension, treatment D.

Methods: This study used a single-center, open, randomized, 4 x 4 Latin Square crossover design in healthy male volunteers. All volunteers were dosed with 200 mg of modafinil on 4 occasions during 4 treatment periods, which were:

Reference Treatment (Treatment A)	2 x 100 mg modafinil tablets (Lot No. 1538-FK1; used in clinical trials); MACORS, FRANCE.
Test Treatment (Treatment B)	2 x 100 mg modafinil tablets (Lot No. 1538-FL5; commercial tablets)
Test Treatment (Treatment C)	1 x 200 mg modafinil caplets (Lot No. 1538-FL6; commercial caplets)
Aqueous Suspension (Treatment D)	200 mg micronised modafinil (Lot No. 95C001/1538-PA009) in an aqueous suspension vehicle [REDACTED]

Modafinil pharmacokinetics for each treatment were evaluated after administration of a single oral dose to 24 volunteers aged between 18 and 45 years and within 15% of ideal body weight. Following overnight fasting, modafinil (a caplet or two tablets) was administered as a single 200 mg dose with 180 mL water on each dosing occasion. For Treatment D, 30 mL of an aqueous suspension containing 200 mg of modafinil in a glass was ingested in one swallow. The glass was thoroughly rinsed with 30 mL of water for 3 times to remove the residual suspension from the glass. Following each rinse, the volunteer drank the rinsed suspension. There was at least a 6-day wash-out period between dosing of any of the 2 treatments.

Blood samples (1x10 mL) for preparation of plasma were collected into lithium heparin Vacutainer tubes by venipuncture of the antecubital veins immediately before dosing and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours (hr) post-dose in each treatment period.

Results (Attachment 18) and Conclusions:

The results demonstrated that Treatment A (2x100 mg Macors tablets in clinical trials), Treatment B (2x100 mg Circa tablets to be marketed), and Treatment C (200 mg caplets to be marketed) are bioequivalent to each other. 90% confidence interval comparisons between Treatment A and B, B and C, and C and A were all within 80-125% ranges for AUC_{0-t} , AUC_{0-inf} , and C_{max} . The results also indicated that the relative bioavailability of modafinil tablet versus micronized aqueous suspension was close to 100%.

Comments:

See the Dissolution section and Formula in Appendix for the dissolution and formula for each biobatch.

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Results: All 24 subjects completed the study. The pharmacokinetic and statistical results are summarized as follows:

Pharmacokinetic Parameter	Treatment B (Test 2x100 mg) ^a	Treatment A (Control 2x100 mg) ^a	90% CI ^b on Non-Transformed Data	90% CI ^b on Log-Transformed Data
AUC ₀₋₄ (μg·hr/mL) ^c	52.8 ± 9.2	53.3 ± 10.1	96.4 - 102	96.5 - 102
AUC _{0-∞} (μg·hr/mL) ^d	56.1 ± 10.3	56.5 ± 11.5	96.6 - 102	96.8 - 102
C _{max} (μg/mL) ^e	4.39 ± 0.74	4.46 ± 0.69	93.4 - 104	93.4 - 103
T _{max} (hr) ^f	2.2 ± 1.1	1.8 ± 1.0	94.5 - 151	NA ^g
t _{1/2} (hr) ^h	11.2 ± 2.0	11.4 ± 2.1	94.1 - 101	NA

Pharmacokinetic Parameter	Treatment C (Test 200 mg) ^a	Treatment A (Control 2x100 mg) ^a	90% CI ^b on Non-Transformed Data	90% CI ^b on Log-Transformed Data
AUC ₀₋₄ (μg·hr/mL) ^c	53.5 ± 8.9	53.3 ± 10.1	97.7 - 103	97.8 - 103
AUC _{0-∞} (μg·hr/mL) ^d	56.9 ± 9.9	56.5 ± 11.5	98.1 - 103	98.3 - 104
C _{max} (μg/mL) ^e	4.42 ± 0.62	4.46 ± 0.69	94.2 - 104	94.6 - 105
T _{max} (hr) ^f	2.0 ± 1.2	1.8 ± 1.0	82.0 - 139	NA ^g
t _{1/2} (hr) ^h	11.4 ± 2.1	11.4 ± 2.1	96.4 - 104	NA

Pharmacokinetic Parameter	Treatment B (Test 2x100 mg) ^a	Treatment C (Test 200 mg) ^a	90% CI ^b on Non-Transformed Data	90% CI ^b on Log-Transformed Data
AUC ₀₋₄ (μg·hr/mL) ^c	52.8 ± 9.2	53.5 ± 8.9	98.7 - 104	98.7 - 104
AUC _{0-∞} (μg·hr/mL) ^d	56.1 ± 10.3	56.9 ± 9.9	98.8 - 104	98.9 - 104
C _{max} (μg/mL) ^e	4.39 ± 0.74	4.42 ± 0.62	95.6 - 106	96.2 - 106
T _{max} (hr) ^f	2.2 ± 1.1	2.0 ± 1.2	66.7 - 113	NA ^g
t _{1/2} (hr) ^h	11.2 ± 2.0	11.4 ± 2.1	98.6 - 106	NA

^a All parameter values are presented as arithmetic mean ± SD (n=24).

^b CI = confidence interval.

^c Area under plasma concentration versus time curve from time zero to the last quantifiable concentration.

^d Area under plasma concentration versus time curve from time zero to infinity.

^e Maximum observed plasma concentration.

^f Time to observed C_{max}. T_{max} values between formulations were not different (Treatment A versus C, p = 0.55; Treatment B versus C, p = 0.46) using the Friedman's Chi-square test.

^g NA = not applicable

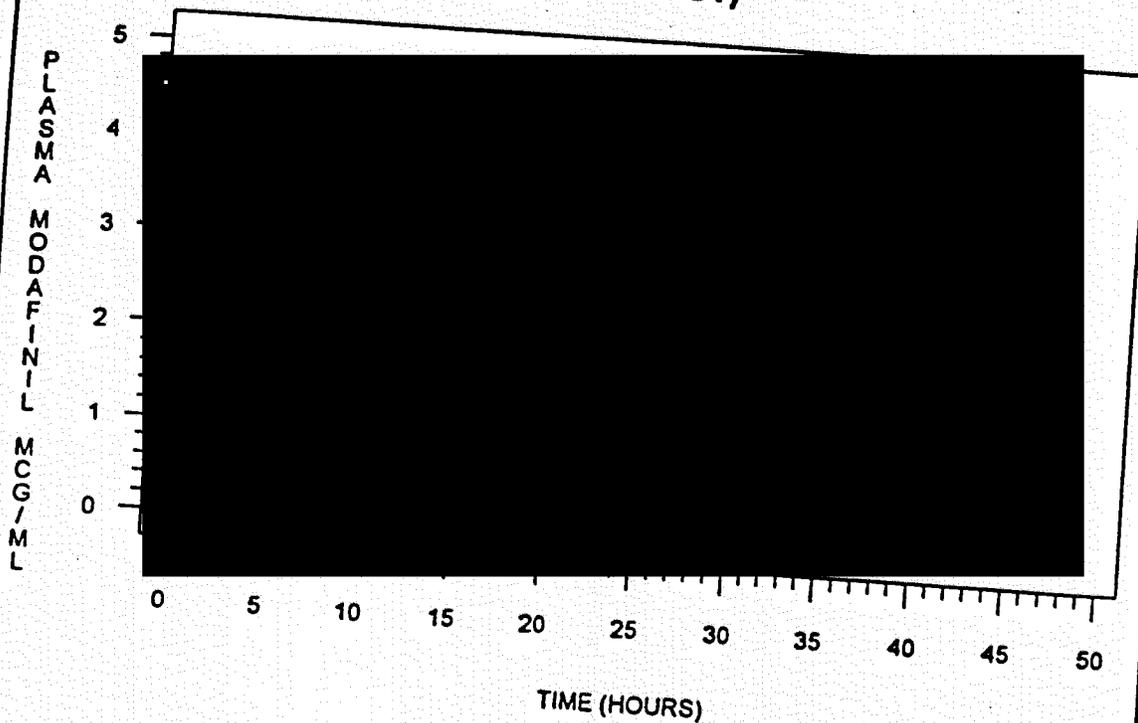
^h Terminal half-life.

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MODAFINIL BIOEQUIVALENCE STUDY
CEPHALON PROTOCOL NO. C1538a/110/BE/UK
SUMMARY

MODAFINIL MEAN DATA

(LINEAR PLOT)

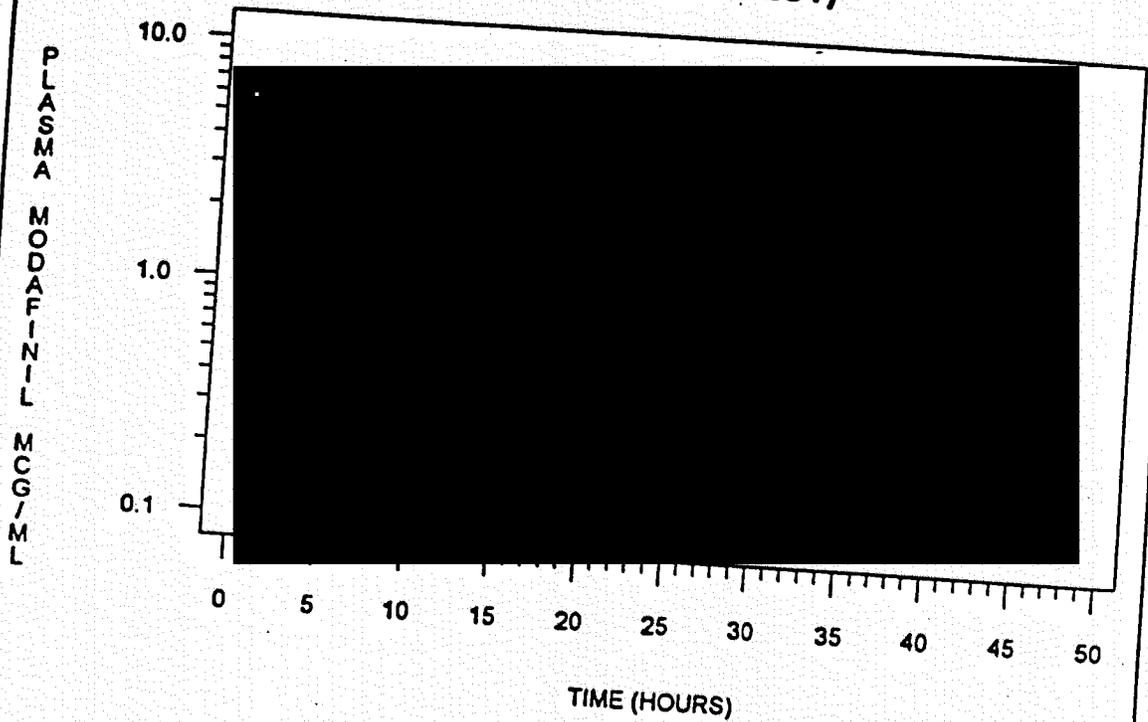


- — ○ — ○ CONTROL 2X100
- — □ — □ TEST 2X100
- △ — △ — △ TEST 200
- ≡ — ≡ — ≡ SUSPENSION

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MODAFINIL BIOEQUIVALENCE STUDY
CEPHALON PROTOCOL NO. C1538a/110/BE/UK
SUMMARY

MODAFINIL MEAN DATA
(SEMI-LOGARITHMIC PLOT)



- — ○ — ○ CONTROL 2X100
- — □ — □ TEST 2X100
- △ — △ — △ TEST 200
- ≡ — ≡ — ≡ SUSPENSION

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57 pages

TRADE Secret

/ Confidential /

Commercial

Appendix E. PK Labeling Proposed By the Sponsor

12 pages

DRAFT

Labeling

APPENDIX F. STUDIES NOT REVIEWED

1 page

Confidential
Commercial

COMPLETED OCT 29 1998

OCT 27 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-717

PROVIGIL® (Modafinil)

(100 mg, 200 mg)

Type of submission: Amendment

Submission Date: March 30, 1998

Sponsor: Cephalon Inc., West Chester, PA

INDICATION: Narcolepsy

REVIEWER: Rae Yuan, Ph.D.

This submission is a response to the approvable letter from our agency dated December 29, 1997. Two issues have been responded to in the submission: 1) interconversion between the enantiomers of modafinil, and 2) drug interaction of modafinil with other major metabolic enzymes, specifically, CYP2C19 and CYP3A. On Sept 23, 1998, a meeting between the sponsor and the agency was held to discuss further evaluations on drug-drug interactions. Three drug interaction studies were proposed and discussed during the meeting:

- 1) In vitro study of modafinil and modafinil sulfone effects on CYP2C19 substrate (clomipramine) metabolism in microsomes obtained from CYP2D6 poor-metabolizers, extensive-metabolizers and super-metabolizers;
- 2) Clinical study of modafinil effect on CYP3A4 substrate, ethinylestradiol;
- 3) Clinical study of modafinil effect on CYP2C9 substrate, S-Warfarin.

The rationales for studies (1) and (2) were based on previous in vitro evidence and case reports (see OCPB review dated Nov 17, 1997 for details). The inhibitory effect of modafinil on CYP2C9, as stated by the sponsor during the September meeting, was discovered recently in an in vitro study (data not submitted yet).

The outline of these three studies has been reviewed. The concerns of the reviewer on the studies were communicated to the sponsor during the meeting, especially regarding the specificity of using ethinylestradiol as an in vivo CYP3A4 substrate. Additional CYP3A4 substrate, midazolam, was suggested by the reviewer during the meeting. The sponsor agreed to submit a detailed study protocol for review.

Comment:

The enantiomer issue was discussed within the OCPB review team. We consider the sponsor's response acceptable.

Recommendations:

The sponsor has designed three drug interaction studies to address the concerns raised in agency's Dec 29th letter. The three proposed studies are acceptable, provided that the study protocol (to be submitted in the future) incorporates the reviewer's comments. The response to the enantiomer issue and dissolution change is acceptable.

Rae Yuan, Ph.D.

/s/ [REDACTED]

Team Leader: Chandra Sahajwalla, Ph.D.

/s/ [REDACTED]

10/26/98

10/27/98

Date of Signature: 10/27/98

Office of Clinical Pharmacology and Biopharmaceutics/Division I

CC list: HFD-120; CSO; HFD-860 (Yuan, Sahajwalla, Mehta); CDR (Barbara Murphy)

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