

**Section 7.2.3.1 Study MOD-024:**

This was a double blind, randomized, crossover trial of modafinil versus placebo performed in France by Dr. F. Laffont. Forty patients were included in the data base; thirty-four with Gelineau's syndrome [narcolepsy] and six with "simple or atypical" hypersomnia. Study results are based on thirty-four of the Gelineau's syndrome patients (four were excluded from the final analysis due to deviations from the overall mean results for efficacy parameters of greater than two standard deviations) and all six of the other hypersomnia patients. The study lasted for six weeks and included: a treatment free reference period (15 days); two double blind treatment periods (each 15 days) during which patients received either modafinil (100 mg morning and midday) or placebo (morning and midday) followed by crossover in the next period; and, an additional open treatment period (15 days) at 300 mg modafinil (200 mg morning and 100 mg midday) for patients with unsatisfactory results during Periods 2 and 3.

Efficacy analyses documented the following for patients with Gelineau's syndrome:

- The number of nocturnal awakenings was less with modafinil compared with both the treatment-free and placebo periods; but this did not reach statistical significance.
- There was a statistically significant ( $p < 0.025$ ) decrease in the number of yawns with modafinil compared to placebo.
- There was a statistically significant ( $p < 0.05$ ) decrease in the number of diurnal sleep attacks with modafinil compared to placebo
- Modafinil did not affect nocturnal sleep time.
- Analysis showed no statistically significant difference between the periods for the number of cataplectic spells. However, patients whose concurrent tricyclic antidepressant treatment could not be discontinued were able to maintain a constant minimal dosage throughout the trial.
- Analysis showed no statistically significant difference between the periods for sleep onset latency.
- 20/30 patients preferred the modafinil period; 3 preferred the placebo period; 7 expressed no preference.

For patients with simple or atypical hypersomnia:

- The number of diurnal sleep attacks decreased significantly with modafinil.
- There was no significant difference in the total nocturnal sleep time.
- The number of yawns decreased statistically significantly with modafinil in comparison to placebo.

- 4/6 patients preferred the modafinil period and 2 expressed no preference.

### **Section 7.2.3.2 Study MOD-025:**

This was a multicenter, controlled, double blind, crossover study versus placebo performed in France and Canada. Sixty-six patients with Gelineau's syndrome were included in the data base. Two patients were excluded due to incorrect inclusion by the investigator; however, for one of these patients, the information does appear in the data listings. A third patient participated in the early part of the study, then withdrew due to stress related to diagnosis of Wolff-Parkinson-White syndrome. He later insisted on being reinstated in the study. Only the earlier data for this patient was included in the analyses. Each patient received 300 mg modafinil/day in two divided doses, morning and midday, as either 100/200 or 200/100 for two weeks. These treatment periods were preceded by a two week run-in period on placebo and each treatment period was separated by a two week washout period on placebo.

For the 63 patients analyzed, the following results were found:

- Based on vigilance diaries, while on modafinil, patients experienced a statistically significant decrease in the duration of daytime sleep periods ( $p = 0.002$ ), the number of desires to sleep ( $p = 0.002$ ), and the number of awakenings during sleep ( $p = 0.05$ ).
- Results from these diaries also noted no significant effect demonstrated in the duration of sleep periods, the duration of periods of wakefulness during sleep, or the number of cataplectic attacks.
- There was a statistically significant ( $p < 0.001$ ) increase in the sleep latency with modafinil on the MWT.
- There were no significant differences between modafinil and placebo in the following parameters on the sleep questionnaire: sleep time, ease of falling asleep, depth of sleep, recuperative quality of sleep, number of dreams, occurrence of pleasant dreams, estimation of sleep time, and occurrence of spontaneous awakenings.
- On a visual analogue scale for symptoms, there was no significant difference between the changes produced by modafinil and placebo in the following parameters: irritable, well, tired, drowsy.
- Also on a visual analogue scale, the overall therapeutic effect, as judged by the doctor and the patient, was statistically significant for modafinil (doctor,  $p = 0.0009$ ; patient,  $p = 0.0005$ ).
- In the modafinil/placebo sequence, 14 patients preferred modafinil, 7 preferred placebo, and 1 did not express a preference; 22 wished to continue, 6 did not.
- In the placebo/modafinil sequence, 20 patients preferred modafinil, 4 preferred

placebo, and 1 did not express a preference; all wished to continue.

### **Section 7.2.3.3 Study MOD94003:**

This was a controlled, randomized, three period, cross-over study versus placebo performed in Canada. Seventy-five patients with narcolepsy were enrolled and 71 completed the full six weeks. One patient dropped out after baseline, not wishing to undergo the tests again. The other three patients dropped out due to adverse events: headache, anxiety, nausea and tics after two days on modafinil 400 mg; rash and mouth ulcers on placebo; and, chest pain on placebo. Patients received modafinil 200 mg, 400 mg or placebo in divided doses (morning and noon) for fourteen days.

For the patients analyzed, the following results were found:

#### **Primary:**

- Modafinil 200 mg and 400 mg significantly increased the mean sleep latency compared to placebo on the MWT by 40% ( $p = 0.0002$ ) and by 54% ( $p = 0.0001$ ), respectively, with no difference between the two doses; no significant carry-over effect was detected ( $p = 0.593$ ).
- Based on patient diaries, modafinil 200 mg and 400 mg significantly reduced the mean number of periods of sleep episodes and severe somnolence by 24% ( $p = 0.013$ ) and by 26% ( $0.007$ ), respectively, with no difference between the two doses. No significant carry-over effect was detected ( $p = 0.815$ ).

#### **Secondary:**

- On the ESS, modafinil 200 mg ( $p = 0.018$ ) and 400 mg ( $p = 0.0009$ ) both decreased the likelihood of falling asleep as measured by the total sleepiness score.
- The following results were from the FCRT which was not defined in the submission; nor were the exact nature of the individual results. Performance improved at 3 hours on both doses of modafinil, but not on placebo. Compared to placebo, patients had 41% fewer gaps on modafinil 200 mg ( $p = 0.026$ ) and 44% fewer gaps on 400 mg ( $p = 0.027$ ). A decrease in the corresponding number of errors was not statistically significant. At 15 hours and 30 minutes, reaction times were slightly (11%) faster for both modafinil doses compared to placebo ( $p = 0.061$  for 200 mg;  $p = 0.051$  for 400 mg).
- Actigraphy results were not available at the time of NDA submission.
- Based on the Global Evaluation, for the patients who had not taken stimulant medication prior to the study, a comparative decrease in excessive daytime somnolence was reported by 80% of patient on modafinil 400 mg, 66% on modafinil 200 mg, and 34% on

placebo. For the patients who had been taking stimulants prior to the study, a comparative decrease in excessive daytime somnolence was reported by 53% of patients on modafinil 400 mg, 50% on modafinil 200 mg, and 25% on placebo. The percentage of patients reporting a deterioration on study medication was: placebo 58%, modafinil 200 mg 25%; and, modafinil 400 mg 33%.

- As a first choice, 50% of patients preferred the 400 mg period, 34% the 200 mg period, and 16% the placebo period. As a first or second choice, 80% of patients selected the 400 mg dose, 84% the 200 mg dose, and 36% the placebo period.

#### **Section 7.2.3.4 Study MOD-026:**

This was an uncontrolled, open label study of the treatment of Gelineau's syndrome and idiopathic hypersomnia performed in France. Fifty-six patients (26 with narcolepsy and 30 with idiopathic hypersomnia) were treated with single or divided daily doses of 100 mg to 400 mg of modafinil for from one month to three years.

The sponsor reports that, "Clinical assessment showed marked therapeutic effects or excellent results, based on elimination of symptoms." [Item 8, Vol. 2, p. 00452]

#### **Section 7.2.3.5 Study MOD-027:**

This was an uncontrolled, open label study of the treatment of narcolepsy and idiopathic hypersomnia performed in France. Fifty-eight patients (48 with narcolepsy with cataplexy, 3 with narcolepsy without cataplexy, and 7 with idiopathic hypersomnia) were treated with single or divided daily doses of 200 mg to 400 mg of modafinil for up to four years.

The sponsor reports that, "Modafinil was effective for daytime somnolence and sleep attacks in narcolepsy patients with and without cataplexy, and in patients with hypersomnia." [Item 8, Vol. 2, p. 00453]

#### **Section 7.2.3.6 Study MOD-028:**

This was an uncontrolled, open label study of the treatment of narcolepsy and idiopathic hypersomnia performed in France. A total of 319 patients (242 with narcolepsy, 59 with idiopathic hypersomnia, 17 with other diagnoses, and 1 with an unspecified diagnosis) were treated with daily doses of 50 mg to 600 mg of modafinil for from one month to ten years.

The sponsor reports that, "Episodes of daytime somnolence resolved in 75% of patients treated with modafinil." [Item 8, Vol. 2, p. 00454]

### **SECTION 7.2.4 OTHER CLINICAL TRIALS:**

In addition to the pivotal and supportive trials described above, there another 143 studies performed by Cephalon or Lafon in normal volunteers, patients with narcolepsy or hypersomnia, or in patients with other disorders. These disorders included: other sleep

disorders, memory disorders, mood disorders, psychomotor disorders, addictive behavior, genitourinary disorders and respiratory disorders.

The results of these studies will not be discussed further in the efficacy portion of this review. They will, however, be discussed in the safety section which follows.

Graphical and tabular summaries of the complete set of clinical trials performed with modafinil were provided by the sponsor and have been reproduced as Appendix I of this review.

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## SECTION 8.0 SAFETY FINDINGS

### SECTION 8.1 METHODS:

The safety of modafinil in the treatment of narcolepsy has been evaluated in 59 clinical pharmacology studies (12 Cephalon\*, 47 non-Cephalon), 6 controlled trials in narcolepsy patients (2 Cephalon, 4 non-Cephalon), 7 non-Cephalon uncontrolled trials in narcolepsy plus the 2 ongoing open label extensions of the Cephalon controlled trials (through June 15, 1996 cut-off date), 52 controlled trials in non-narcolepsy patients (all non-Cephalon), and 25 uncontrolled trials in non-narcolepsy patients (also all non-Cephalon). Nine of the non-Cephalon trials are ongoing (2 controlled in narcoleptics, 3 uncontrolled in narcoleptics, and 4 controlled in non-narcolepsy patients). Limited safety information is available for many of the non-Cephalon sponsored studies due loss of the CRF's for those studies. [based on sponsor's faxed data dated 9/8/97]

- \* This number includes the completed portions of abuse liability study (201) and the clinical pharmacology portions of the controlled narcolepsy studies (301 and 302).

The sponsor has divided the data on which the ISS is based into three separate sources:

- 1 ) Cephalon sponsored, controlled, multicenter, Phase 3 studies in patients with narcolepsy; this includes double-blind and open label treatment periods through June 15, 1996;
- 2 ) Individual Cephalon sponsored Phase 1 and 2 clinical pharmacology studies;
- and, 3 ) AE, dosing and limited demographic information from all foreign, non-Cephalon sponsored, clinical studies with supporting CRF's; the data from these foreign studies are subdivided into those studies with subjects who have narcolepsy and/or hypersomnia (NA/HS) and those subjects with other disorders.

The sponsor used the COSTART classification system for coding the actual AE's as written on the CRF to the preferred terms.

This review of the safety of modafinil in the exposed population is centered on the information provided by the sponsor in the Integrated Summary of Safety and the study summaries for the above noted trials. In addition, narrative summaries of deaths, serious adverse events and discontinuations were reviewed. Finally, many of the original tabular summaries were examined in their entirety.

### SECTION 8.2 SERIOUS ADVERSE EVENTS:

#### SECTION 8.2.1 DEATHS:

There were no deaths in Cephalon sponsored studies.

Four deaths were included in the safety data base (one modafinil treated subject in each of four studies) for the foreign, non-Cephalon sponsored studies. For Subject 602, Study P1439, the data base listed the cause of death as "asthenia." However, the patient narrative listed the cause of death as "myocardial infarction." An additional death was documented in the narratives (Subject 16, Study MOD-021), but had not been included in the safety data base.

The following table (sponsor's Table 8.9-22. "Listing of Subject Deaths"; Item 8, Vol. 3, p. 01046) summarizes the available information regarding the five deaths.

**Table 32. Deaths: All Studies**

Study	Subject Information (age, gender, indication)	Dose (mg/d)	Duration of Therapy (d)	AEs Preceding Death (by COSTART Terms)	Severity	Relatedness
MOD-032	Subject K4 40 yrs, F Amyotrophic Lateral Sclerosis	200	Unknown	Aggravation Reaction	Severe	Not Related
MOD-035	Subject 101 82 yrs, F Depression	150	1	Heart Failure Pain Kidney Function Abnormality	Life-Threatening	Not Related
				Flatulence	Unknown	Unknown
Open/2-1	Subject CR04 65 yrs, F Major Depressive Episode	200	Unknown	Syncope Dyspnea	Life-Threatening	Unknown
P1439	Subject 602 68 yrs, F Age-assoc. Memory Impairment	400	Unknown	Asthenia <sup>1</sup>	Unknown	Unknown
MOD-021 <sup>2</sup>	Subject 16 58 yrs, M Major Depressive Episode	200	8	Aggravation of Encephalopathy	NE	Not Related <sup>3</sup>

Source: Table Following Text 23.2.0.

Abbreviations:

COSTART = Coding Symbols for Thesaurus of Adverse Reaction; F = female; NE = not evaluated.

<sup>1</sup> Database indicated asthenia as the cause of death; actual cause of death according to patient narrative was due to myocardial infarction.

<sup>2</sup> Subject death not listed in database; information obtained from narrative.

<sup>3</sup> Narrative indicated that "advanced cirrhosis of the liver could be totally responsible for the outcome."

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**SECTION 8.2.2 NON-FATAL SERIOUS ADVERSE EVENTS:**

Fourteen subjects (9 modafinil treated and 5 placebo treated) reported SAE's in the Cephalon Phase 3 studies. Three subjects (3 modafinil treated and 0 placebo treated) reported SAE's in the Cephalon Phase 1 and 2 studies. Nine subjects (6 modafinil treated and 3 placebo treated) reported SAE's in the foreign, non-Cephalon sponsored studies in subjects with NA/HS. Forty-three subjects (29 modafinil treated and 14 placebo treated) reported SAE's in the foreign, non-Cephalon sponsored studies in subjects with disorders other than NA/HS.

Of the SAE's reported, 32 were judged by the investigators to be possibly related, probably related, or related to study drug. Sixty-three percent (20/32) were judged to be probably related and 34% (11/32) possibly related. One SAE (dyspnea; Study C1538a/301NA/US) was judged to be related to study drug. Twelve of these 32 (38%) SAE's occurred in placebo treated subjects.

The following table (sponsor Table 8.9-16. "SAEs Related to Treatment [Possible, Probable, or Related] - By Study"; Item 8, Vol. 3, pp. 01029-01030) summarizes the available information regarding SAE's.

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Table 33. Serious Adverse Events: All Studies

Study Subset Study Number	Patient No.	COSTART Term	Treatment / Dose (mg/d)	Investigator's Causality Assessment	Day of Onset	Outcome
<b>Cephalon Phase 3 Double-Blind</b>						
C1538a/301/NA/US	409	Chest Pain	Modafinil 400	Probable	10	Resolved w/o Residual
	410†	Leukopenia*	Modafinil 400	Possible	-1	Resolved w/o Residual
	1305	Dyspnea	Modafinil 400	Related	3	Resolved w/o Residual
C1538a/302/NA/US	903	Ventricular Extrasystoles	Modafinil 400	Possible	50	Continuing
	903	Palpitation	Modafinil 400	Possible	50	Continuing
	2010	Hypoventilation	Modafinil 200	Possible	62 †	Resolved w/o Residual
<b>Cephalon Phase 1/2</b>						
CEP-2101	16	ECG Abnormal	Modafinil 400	Possible	7	Resolved w/o Residual
	19	Tachycardia	Modafinil 800	Probable	1	Continuing
C1538a/102/NA/US	78	Psychosis	Modafinil 600	Probable	12	Resolved w/o Residual
<b>Foreign, Non-NA/HS</b>						
876	K-06	Aggravation Reaction	Placebo	Probable	not known	Continuing
	S-04	Agitation	Modafinil 300	Probable	171	Continuing
	S-04	Hostility	Modafinil 300	Probable	171	Continuing
908	E1106	Liver Function Tests Abnormal	Placebo	Probable	not known	Resolved w/o Residual
	D1104	Personality Disorder	Placebo	Possible	1	Continuing
	D1103	Breast Neoplasm	Modafinil 300	Possible	42	Continuing

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**Table 33. Serious Adverse Events: All Studies (continued)**

Study Subset Study Number	Patient No.	COSTART Term	Treatment / Dose (mg/d)	Investigator's Causality Assessment	Day of Onset	Outcome
P1425	29-1	Hypertension	Modafinil 400	Probable	7	Resolved w/o Residual
	1-03	Anxiety	Modafinil 400	Possible	4	Continuing
	4-02	Anxiety	Modafinil 400	Possible	5	Continuing
	4-06	Anxiety	Modafinil 400	Probable	1	Continuing
	12-1	Anxiety	Placebo	Probable	5	Continuing
	19-3	CNS Stimulation	Placebo	Probable	9	Continuing
	1-03	Confusion	Modafinil 400	Possible	4	Continuing
	12-1	Hostility	Placebo	Probable	5	Continuing
	4-06	Insomnia	Modafinil 400	Probable	1	Continuing
	4-06	Nervousness	Modafinil 400	Probable	1	Continuing
	19-3	Nervousness*	Placebo	Probable	9	Continuing
	19-1	Nervousness*	Placebo	Probable	9	Continuing
	12-1	Nervousness*	Placebo	Probable	5	Continuing

Source: Tables Following Text 15.1.0 and 15.2.0; Appendix 8.D.1 and 8.D.2.

Notes: Table presents SAEs judged to be related (i.e., defined as related, probably related, or possibly related) to study medication administration.

**Abbreviations:**

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; w/o = without.

\* 2 SAEs reported in one patient at this dose with this causality and outcome.

† Includes occurrences of leukopenia and neutropenia, both coded to 'leukopenia' under COSTART. Following identification of this case, a review of all laboratory values for the double-blind studies for neutrophil values  $\leq 1000/\text{mm}^3$  (as a post-baseline event in the absence of pre-existing depressed neutrophil count) showed 3 cases in modafinil-treated patients and 2 placebo-treated patients (refer to Hematology section [Section 8.9.9.2]).

**SECTION 8.3 ASSESSMENT OF DROPOUTS:**

**SECTION 8.3.1 MODAFINIL EXPOSURE:**

A total of 2305 subjects were treated with modafinil for a total of 497 subject-years. For subjects with narcolepsy/hypersomnia, exposure includes a total of 412 subject-years, 61 subject-years in the Cephalon Phase 3 double-blind studies and 351 subject-years in the foreign, non-Cephalon sponsored studies. Most of these subjects received doses between 200 and 400 mg/d and were treated for 90 days or less. In the Cephalon Phase 1/2 studies, 232 subjects received modafinil at doses between 200 and 800 mg/d, and 94% of these subjects were treated for fewer than 14 days. Some subjects in the foreign, non-Cephalon sponsored studies were treated with doses of more than 1000 mg/d. The following table (sponsor's Table 8.9-2. "Summary of Duration of Modafinil Use by Mean Daily Dose - Overall Exposure"; Item

8, Vol. 3, p. 00976) summarizes modafinil exposure by specified durations, at specified mean total daily doses, in specified study subsets. This table does not take into account the upward dose titration (one week at 100 mg) in Cephalon Study 302. The sponsor notes that insufficient information was available to determine whether all subjects in the foreign, non-Cephalon sponsored studies were unique. It should also be noted that a single daily dose was administered in the Cephalon sponsored studies, while a split dose (morning and noon) was often administered in the non-Cephalon sponsored studies.

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Table 34. Overall Exposure by Mean Daily Dose

Study Subset	Duration (days)	Number of Subjects										
		Mean Total Daily Dose (mg)									Total M	Grand Total
		Placebo*	<175	175-224	225-374	375-424	425-999	≥1000	Unknown Dose M			
Cephalon Phase 3 Double-Blind	<14	4	0	5	0	12	0	0	0	0	17	21
	14-28	1	0	3	0	5	0	0	0	0	8	9
	29-90	180	0	177	0	167	0	0	0	0	344	524
	Total	185	0	185	0	184	0	0	0	0	369	554 <sup>1</sup>
Cephalon Phase 1/2	<14	22	0	132	1	22	62	0	0	0	217	239
	14-28	6	0	0	0	11	4	0	0	0	15	21
	Total	28	0	132	1	33	66	0	0	0	232	260 <sup>2</sup>
Foreign, NA/HS	<14	0	2	6	4	0	0	0	0	0	12	12
	14-28	2	3	23	87	1	0	0	0	0	114	116
	29-90	0	7	41	29	2	1	0	2	2	82	82
	91-179	0	9	53	24	0	1	0	2	2	89	89
	180-364	0	4	31	27	4	0	0	0	0	66	66
	≥365	0	11	23	41	9	4	0	3	3	91	91
	Unknown	1	0	0	0	0	0	0	79	79	79	80
	Total	3	36	177	212	16	6	0	86	86	533	536 <sup>3</sup>
Foreign, non-NA/HS	<14	115	72	242	60	88	62	13	3	3	540	655
	14-28	136	56	119	42	53	14	1	1	1	286	422
	29-90	112	42	38	150	8	7	0	1	1	246	358
	91-179	23	0	4	10	7	0	0	1	1	22	45
	180-364	21	0	25	27	0	0	0	0	0	52	73
	Unknown	12	0	0	0	0	0	0	25	25	25	37
	Total	419	170	428	289	156	83	14	31	31	1171	1590 <sup>4</sup>
	All Studies	<14	141	74	385	65	122	124	13	3	3	786
14-28		144	59	145	129	70	18	1	1	1	423	567
29-90		292	49	256	179	177	8	0	3	3	672	964
91-179		23	9	57	34	7	1	0	3	3	111	134
180-364		21	4	56	54	4	0	0	0	0	118	139
≥365		0	11	23	41	9	4	0	3	3	91	91
Total		1021	365	1262	507	441	233	26	133	133	3079	3752

Table 34. Overall Exposure by Mean Daily Dose (continued)

Study Subset	Duration (days)	Number of Subjects									
		Mean Total Daily Dose (mg)									
		Placebo*	<175	175-224	225-374	375-424	425-999	≥1000	Unknown Dose M	Total M	Grand Total
	Unknown	13	0	0	0	0	0	0	104	104	117
	Total	635	206	922	502	389	155	14	117	2305	2940 <sup>s</sup>

Source: Tables Following Text 2.2.1, 2.3.1, 2.5.1, and 2.6.1. The All Studies category includes data from Cephalon Phase 3 Double-Blind studies, Cephalon Phase 1/2 studies, foreign, non-Cephalon-sponsored studies in subjects with NA/HS, and foreign, non-Cephalon-sponsored studies in subjects with disorders other than NA/HS.

1 Cephalon Phase 3: There are 4 subjects that received no drug.

2 Cephalon Phase 1/2: There are 11 subjects that received other drug(s).

3 Foreign, NA/HS: There are 3 subjects that received unknown drug.

4 Foreign, non-NA/HS: There are 10 subjects that received unknown drug.

5 All Studies: There are a total of 28 subjects that received either no, other, or unknown drug.

6 Numbers of subjects listed in the placebo column represent those who received placebo only; subjects who received both placebo and modafinil appear in the modafinil columns.

Notes: Exposure in Cephalon Phase 3 Double-Blind studies represents information only from the 9-week double-blind treatment period. Data from the Cephalon Phase 3 Open-Label studies are excluded; these data are provided in Table 8.9-3 and Table Following Text 2.8.1. The 40-week continuation and 48-week extension open-label treatment periods are ongoing.

Abbreviation:  
M = modafinil

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With the inclusion of Cephalon Phase 3 open label data, the number of subjects in various study subsets treated with modafinil for six months or greater and for one year or greater is summarized in the table which follows (sponsor's Table 8.9-3. "Number of Subjects Exposed to Modafinil for Six Months or Greater and for One Year or Greater"; Item 8, Vol. 3, p. 00979).

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Table 35. Long Term Exposure

Study Subset	Modafinil Dose and Duration			
	200 to 400 mg/d		All Dose Levels	
	≥ 6 months	≥ 1 year	≥ 6 months	≥ 1 year
All Studies	537	207	559	225
Cephalon Phase 3 Studies (Double-Blind and Open-Label)	350	134	350	134
Cephalon Phase 1/2 Studies	0	0	0	0
Foreign, NA/HS Studies	135	73	157	91
Foreign, non-NA/HS Studies	52	0	52	0

Source:

Tables Following Text 2.0.1, 2.1.1, 2.2.1, 2.3.1, 2.4.1, 2.5.1, 2.6.1, and 2.8.1.

Notes:

≥ 6 months is defined as ≥ 180 days.

≥ 1 year is defined as ≥ 336 days (48 weeks or 12 x 28-day months) for the Cephalon-sponsored studies and ≥ 365 for the foreign, non-Cephalon-sponsored studies.

It should be noted that data from the 9-week double-blind, 2-week withdrawal (applicable to Study C1538a/302/NA/US only), and 40-week open-label continuation (through the data acquisition cut-off date of 15 June 1996) treatment periods are included in this exposure table. The 40-week continuation and 48-week extension open-label treatment periods are ongoing.

## SECTION 8.3.2 ADVERSE EVENTS:

The sponsor has provided the following table (sponsor's Table 8.9-18. "AEs in Subjects Who Discontinued Due to AEs - By COSTART Terms"; Item 8, Vol. 3, p. 01034) in the ISS.

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**Table 36. Sponsor's AE Summary for Dropouts Due to AE**

BODY SYSTEM  COSTART Term	Subjects Discontinued Due to Specified AE*							
	N (%)							
	Cephalon Phase 3 Double-Blind		Cephalon Phase 1/2		Foreign, NA/HS		Foreign, non-NA/HS	
	M N=369	P N=185	M N=232	P N=61	M N=533	P N=103	M N=1171	P N=701
<b>NERVOUS SYSTEM</b>	11 (3.0)	2 (1.1)	5 (2.2)	0 (0)	13 (2.4)	0 (0)	75 (6.4)	13 (1.9)
Nervousness	2 (0.5)	0 (0)	1 (<.5)	0 (0)	3 (0.6)	0 (0)	19 (1.6)	5 (1)
Cataplexy	4 (1.1)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Depression	2 (0.5)	0 (0)	0 (0)	0 (0)	3 (0.6)	0 (0)	6 (0.5)	1 (<.5)
Insomnia	1 (<.5)	0 (0)	2 (0.9)	0 (0)	2 (<.5)	0 (0)	25 (2.1)	2 (<.5)
<b>BODY AS A WHOLE</b>	5 (1.4)	1 (0.5)	1 (<.5)	0 (0)	7 (1.3)	1 (1.0)	32 (2.7)	6 (0.9)
Headache	4 (1.1)	0 (0)	1 (<.5)	0 (0)	1 (<.5)	0 (0)	11 (0.9)	0 (0)
<b>DIGESTIVE</b>	4 (1.1)	0 (0)	1 (<.5)	0 (0)	6 (1.1)	1 (1.0)	26 (2.2)	2 (<.5)
Nausea	2 (0.5)	0 (0)	1 (<.5)	0 (0)	3 (0.6)	0 (0)	7 (0.6)	0 (0)
<b>CARDIOVASCULAR</b>	2 (0.5)	0 (0)	1 (<.5)	0 (0)	2 (<.5)	1 (1.0)	12 (1.0)	3 (<.5)
<b>RESPIRATORY</b>	3 (0.8)	0 (0)	0 (0)	0 (0)	1 (<.5)	0 (0)	3 (<.5)	0 (0)

Source: Summarized from Tables Following Text 18.2.0, 18.3.0, 18.5.0, and 18.6.0.

Note: Table represents AEs in subjects who discontinued due to AEs by COSTART terms (presented as AE COSTART categories in which the incidence of occurrence was 0.25% or greater [arbitrary cut-off; 3 subjects or more reporting any AE in Cephalon Phase 3, Cephalon Phase 1/2, and foreign, non-Cephalon-sponsored studies in subjects with NA/HS combined]).

- Multiple AEs may be shown for a subject who discontinued due to AE (for Cephalon-sponsored studies, more than one AE may have been indicated, for foreign, non-Cephalon-sponsored studies, all AEs for a subject who discontinued due to AE are shown as outcome of 'discontinued study' is not included on the adverse event record).

Abbreviations:

COSTART = Coding Symbols for Thesaurus of Adverse Reaction; M = modafinil; P = placebo; N = number.

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It should be noted, however, that this table includes only AE's in which the incidence of occurrence was 0.25% or greater (3 or more subjects reporting any AE in the Cephalon Phase 3, Cephalon Phase 1/2, and foreign, non-Cephalon sponsored NA/HS study subsets combined). As this system may have missed isolated, but clinically significant events, the following table summarizes all AE's which this reviewer considers of potential clinical concern, occurring in all Cephalon and non-Cephalon studies for which CRF's were available. It is based on review of all narrative summaries provided by the sponsor (Item 8, Vol. 76, pp. 32322-32487). It includes AE's which resulted in discontinuation, as well as events not resulting in discontinuation, listed as serious, but designated as unrelated or remotely related to study drug. All serious AE's believed to be related to study drug resulted in discontinuation from the study, as would be expected.

**Table 37. AE's of Potential Clinical Concern (resulting in discontinuation, or considered unrelated or remotely related to study drug)**

AE	Cephalon		non-Cephalon	
	discontinued	un-, remotely related	discontinued	un-, remotely related
hypertension	1	0	2	1
tachycardia	3	0	1	1
chest pain	3	3	1	0
atrial arrhythmia	1	0	0	0
palpitations	3	1	0	2
"cardiovascular disorder"	1	0	0	0
PVC's	2	0	0	0
T-wave changes	0	1	0	0
ECG abnormal	1	0	0	0
myocardial infarction	0	0	0	1
bigeminy	0	1	0	0
8-sec. asystole	0	0	0	1
syncope	0	0	0	1
retinal hemorrhage	0	1	0	0
stroke	1	0	0	0
hallucinations	0	0	0	1
psychosis	1	0	0	0
delirium/confusion	0	0	4	0
buccofacial dyskinesia	0	0	1	0
worsening asthma	2	0	0	0
hypoventilation	1	0	0	0
pneumonia	1	1	0	1
dyspnea	0	1	2	0
hemoptysis	1	0	0	0
melena	1	0	0	0
increased liver enzymes	1	1	1	0
increased alk. phos.	0	0	0	2
leukopenia	1	0	0	0
astrocytoma	0	1	0	0
decreased vision	0	0	0	1

As can be seen, these AE's were, generally, either of unclear relationship to study drug or were isolated events. Of note, close review of each of the events listed in the above table revealed only three which appeared to be clinically significant and clearly related to study drug. All three occurred in Cephalon clinical pharmacology studies.

- 1) *Hypertension*: Subject 23 (21 year old male), Protocol CEP-2101, received 800 mg of modafinil and developed moderate diastolic hypertension (BP before treatment = 125/89 mm Hg supine, 122/91 mm Hg standing; after treatment = 143/103 mm Hg supine, 142/106 standing)
- 2) *Tachycardia*: Subject 23 (21 year old male), Protocol CEP-2101 (*same patient as #1*), received 800 mg of modafinil and developed significant increases in pulse rate (PR) eight hours after first dose (PR before treatment = 77/98, supine/standing; after treatment = 133/147, supine/standing). This subject also reported severe palpitations.
- 3) *Psychosis*: Subject 78 (22 year old male), Protocol C1538a/102/MT/US, had no history of medical or psychiatric disease, received 200 mg modafinil Day 1, 400 mg modafinil Day 2 and 600 mg modafinil Days 3 through 10. He experienced an acute psychotic episode on Day 11 (study drug discontinued) which resolved three days later.

These three AE's each occurred at doses of modafinil which are 1) higher than those studied in the pivotal clinical efficacy/safety studies, and 2) higher than the doses recommended for treatment by the sponsor in the labeling included in this NDA.

#### SECTION 8.4

#### OTHER ADVERSE EVENTS:

##### SECTION 8.4.1

#### ADVERSE EVENTS OVERALL:

There was a higher percentage of subjects reporting AE's in the Cephalon sponsored studies than in the foreign studies. The sponsor believes that this may be due to more highly structured CRF's and reporting procedures used in the U.S. studies. The most frequently reported category of AE's across all studies was the nervous system. Other categories with frequently reported AE's were the digestive system, the cardiovascular system and the respiratory system.

A modest dose response was observed in the Cephalon sponsored studies as a whole. Most of this dose response trend is accounted for by the Phase 1/2 studies which included the evaluation of higher dose levels. Although there were some dose dependent differences in AE's reported in the initial weeks of treatment in the Cephalon Phase 3 studies in some body systems (e.g., digestive, as well as headache and nausea), these differences did not increase as treatment continued. However, dose-dependent increases in new AE's in the digestive system category were noted at each time period. In the cardiovascular system category there was a slight increase in the percentage of modafinil treated subjects reporting new or worsened AE's later in the study. A similar dose response trend was seen in the foreign studies but was less pronounced. In these studies, the percentages of subjects reporting AE's in a given body system category tended to be similar in the placebo group and in all modafinil dose groups, with the exception of the > 425

mg/d group, where the percentages were generally higher. In the Cephalon studies, the percentages of subjects reporting AE's (by body system category) classified as related to study drug were substantially higher in the modafinil treated subjects than in the placebo treated subjects, for the digestive system, the nervous system, the body as a whole, and the cardiovascular system. In the foreign studies, the percentages of subjects reporting AE's classified as related to study medication were similar in the modafinil and placebo treatment groups. The percentages of subjects reporting AE's classified as being of unknown relationship to study medication were consistently higher in the modafinil treated subjects; but this classification, "unknown", was created specifically for the foreign study data base where the question of relatedness was either not addressed or the necessary information was not obtained.

The following table (sponsor's Table 8.9-10. "Most Frequently Reported AE's - By COSTART Term"; Item 8, Vol. 3, pp. 01002) compares AE's between drug and placebo treated subjects. Body system categories in which there was an incidence of occurrence of AE's of at least 10% in all study subsets combined, and COSTART preferred term categories in which there was an incidence of occurrence of at least 2.5% in all study subsets combined are presented.

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**Table 38. Most Frequently Reported AE's - All Study Subsets**

COSTART BODY SYSTEM	Subjects Reporting AEs N (%)							
	Cephalon Phase 3 Double-Blind		Cephalon Phase 1/2		Foreign, NA/HS		Foreign, non-NA/HS	
	M N=369	P N=185	M N=232	P N=61	M N=533	P N=103	M N=1171	P N=701
<b>NERVOUS SYSTEM</b>	109 (30)	41 (22)	109 (47)	20 (33)	86 (16)	8 (8)	419 (36)	167 (24)
Nervousness	30 (8)	12 (6)	33 (14)	3 (5)	23 (4)	1 (<1)	86 (7)	31 (4)
Insomnia	11 (3)	2 (1)	25 (11)	1 (2)	19 (4)	2 (2)	123 (11)	32 (5)
Anxiety	13 (4)	1 (<1)	10 (4)	1 (2)	6 (1)	1 (<1)	87 (7)	20 (3)
Somnolence	7 (2)	4 (2)	27 (12)	16 (26)	6 (1)	2 (2)	26 (2)	29 (4)
CNS Stimulation	0 (0)	0 (0)	4 (2)	0 (0)	7 (1)	0 (0)	78 (7)	22 (3)
Sleep Disorder	2 (<1)	3 (2)	0 (0)	0 (0)	9 (2)	1 (<1)	52 (4)	21 (3)
<b>BODY AS A WHOLE</b>	247 (67)	121 (65)	113 (49)	8 (13)	53 (10)	11 (11)	209 (18)	81 (12)
Headache	183 (50)	74 (40)	95 (41)	6 (10)	23 (4)	3 (3)	101 (9)	33 (5)
Asthenia	6 (2)	3 (2)	17 (7)	1 (2)	9 (2)	2 (2)	57 (5)	27 (4)
Infection	51 (14)	29 (16)	2 (<1)	0 (0)	0 (0)	2 (2)	6 (<1)	1 (<1)
Abdominal Pain	16 (4)	7 (4)	7 (3)	1 (2)	5 (<1)	1 (<1)	41 (4)	6 (<1)
<b>DIGESTIVE</b>	143 (39)	45 (24)	85 (37)	5 (8)	32 (6)	3 (3)	143 (12)	50 (7)
Nausea	47 (13)	7 (4)	47 (20)	2 (3)	8 (2)	0 (0)	46 (4)	14 (2)
Anorexia	17 (5)	2 (1)	25 (11)	1 (2)	6 (1)	0 (0)	32 (3)	4 (<1)
Dry Mouth	19 (5)	1 (<1)	20 (9)	1 (2)	7 (1)	0 (0)	30 (3)	9 (1)

Source: Tables Following Text 10.2.0, 10.3.0, 10.5.0, and 10.6.0.

Abbreviations:

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; M = modafinil; N = number; P = placebo.

Note: Table presents AEs by COSTART preferred term (presented as body system categories in which the incidence of occurrence was 10% or greater [arbitrary cut-off; 74% of subjects reporting any AE] and COSTART preferred term categories in which there is an incidence of occurrence of at least 2.5% [arbitrary cut-off; 90% of subjects reporting any AE]) in all study subsets combined (i.e., Cephalon Phase 3, Cephalon Phase 1/2, foreign, non-Cephalon-sponsored studies in subjects with NA/HS, or foreign, non-Cephalon-sponsored studies in subjects with disorders other than NA/HS).

The sponsor's Table 8.9-11 ("Incidence of Treatment-Emergent AEs Reported by 1% or Greater of Modafinil-Treated Subjects and at Greater Frequency than Placebo-Treated Subjects in Cephalon Phase 3 Double-Blind Studies"; Item 8, Vol. 3, pp. 01004-01005), reproduced below, shows that 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. The most frequent AEs occurring in modafinil treated subjects compared to placebo treated subjects were headache and nausea. The difference between the two treatment groups was comparable in the two Phase 3 studies with the exceptions of headache, observed primarily in Study 301 and respiratory system AE's, observed primarily in Study 302.

**Table 39. AE's Reported by 1% or Greater of Modafinil Treated Subjects and at Greater Frequency than Placebo Treated Subjects - Cephalon Phase 3 Double Blind Studies**

COSTART Body System	COSTART Preferred Term <sup>1</sup>	Treatment Group	
		Modafinil N=369	Placebo N=185
BODY AS A WHOLE	Headache	183 (50)	74 (40)
	Pain Chest	8 (2)	2 (1)
	Pain Neck	6 (2)	2 (1)
	Chills	6 (2)	0 (0)
	Neck Rigid	3 (1)	0 (0)
	Chills Fever	2 (1)	0 (0)
DIGESTIVE	Nausea	47 (13)	7 (4)
	Diarrhea	30 (8)	8 (4)
	Dry Mouth	19 (5)	1 (1)
	Anorexia	17 (5)	2 (1)
	Liver Function Abnormal <sup>2</sup>	10 (3)	3 (2)
	Vomiting	6 (2)	2 (1)
	Ulcer Mouth	5 (1)	0 (0)
	Gingivitis	4 (1)	0 (0)
	Thirst	2 (1)	0 (0)
NERVOUS	Nervousness	30 (8)	12 (6)
	Dizziness	17 (5)	7 (4)
	Depression	14 (4)	5 (3)
	Anxiety	13 (4)	1 (1)
	Cataplexy	12 (3)	4 (2)
	Insomnia	11 (3)	2 (1)
	Paresthesia	10 (3)	1 (1)
	Dyskinesia	6 (2)	0 (0)
	Hypertonia	5 (2)	0 (0)
	Confusion	4 (1)	0 (0)
	Amnesia	3 (1)	0 (0)
	Emotional Lability	3 (1)	0 (0)
	Ataxia	2 (1)	0 (0)
	Tremor	2 (1)	0 (0)

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**Table 39. AE's Reported by 1% or Greater of Modafinil Treated Subjects and at Greater Frequency than Placebo Treated Subjects - Cephalon Phase 3 Double Blind Studies (continued)**

COSTART Body System	COSTART Preferred Term <sup>1</sup>	Treatment Group	
		Modafinil N=369	Placebo N=185
RESPIRATORY	Rhinitis	42 (11)	14 (8)
	Pharyngitis	23 (6)	5 (3)
	Lung Disorder	13 (4)	3 (2)
	Dyspnea	7 (2)	1 (1)
	Asthma	4 (1)	0 (0)
	Epistaxis	3 (1)	0 (0)
CARDIOVASCULAR	Hypotension	6 (2)	2 (1)
	Hypertension	6 (2)	0 (0)
	Vasodilation	5 (1)	0 (0)
	Arrhythmia	2 (1)	0 (0)
	Syncope	2 (1)	0 (0)
UROGENITAL	Urination Abnormal	2 (1)	0 (0)
	Urine Retention	2 (1)	0 (0)
	Ejaculation Abnormal <sup>2</sup>	1 (1)	0 (0)
SPECIAL SENSES	Amblyopia	9 (2)	1 (1)
	Vision Abnormal	7 (2)	0 (0)
SKIN/APPENDAGES	Herpes Simplex	4 (1)	0 (0)
	Skin Dry	3 (1)	0 (0)
METABOLIC/NUTRITIONAL	Hyperglycemia	4 (1)	0 (0)
	Albuminuria	2 (1)	0 (0)
MUSCULOSKELETAL	Joint Disorder	2 (1)	0 (0)

Source: Tables Following Text 6.1.0.

<sup>1</sup>Events reported by at least 1% of PROVIGIL-treated patients that were more frequent than in the placebo group are included; incidence is rounded to the nearest 1%. Patients who had at least one episode of an event during the study period are represented in the table. The adverse experience terminology is coded using a standard modified COSTART Dictionary. Events for which the PROVIGIL incidence was at least 1%, but equal to or less than placebo are not listed in the table. These events included the following: infection, back pain, pain, hypothermia, abdominal pain, flu syndrome, allergic reaction, fever, asthenia, accidental injury, general edema, tachycardia, palpitations, migraine, ventricular extrasystole, bradycardia, dyspepsia, tooth disorder, constipation, flatulence, increased appetite, gastroenteritis, GI disorder, ecchymosis, anemia, leukocytosis, peripheral edema, increased weight, increased SGOT, myalgia, arthritis, arthralgia, somnolence, thinking abnormality, leg cramps, sleep disorder, hallucinations, hyperkinesia, decreased libido, increased cough, sinusitis, bronchitis, pneumonia, rash, sweating, pruritus, skin disorder, psoriasis, ear pain, eye pain, ear disorder, taste perversion, dysmenorrhea<sup>3</sup>, urinary tract infection, pyuria, hematuria, cystitis, and disturbed menses<sup>3</sup>.

<sup>2</sup> Elevated liver enzymes.

<sup>3</sup> Incidence adjusted for gender.

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**SECTION 8.4.2 ADVERSE EVENTS BY GENDER:**

Although there were inconsistent differences in the percentages of female and male subjects reporting AE's in some subcategories of studies (for both the modafinil and placebo treated groups), there were no consistent or significant qualitative differences between female and male subjects in the body system categories of AE's SAE's, or related SAE's reported.

**SECTION 8.4.3 ADVERSE EVENTS BY AGE:**

All subjects less than or equal to 16 years of age were in the foreign studies, in particular the non-NA/HS studies. While the percentage of pediatric subjects reporting AE's was consistently lower than percentage of adult subjects reporting AE's, the total N for the pediatric population is too small for adequate comparison. Fourteen SAE's were reported in the foreign, non-NA/HS studies which all came from one pediatric subject who took twelve 100 mg modafinil tablets in a 15 hour period.

The percentages of adult subjects reporting AE's were greater in the modafinil group than in the placebo group for all study subsets. The percentages of subjects in the adult group reporting AE's classified as serious were similar in the modafinil and placebo groups. With the exception of the foreign, non-NA/HS studies, adult subjects reporting AE's judged as serious and related tended to be in the modafinil treated groups.

The large majority of the geriatric subjects (greater than or equal to 65 years of age) were from the foreign non-NA/HS studies. In those studies, there was a slightly greater percentage of modafinil treated and placebo treated subjects reporting AE's in geriatric subjects compared to the adult and pediatric groups.

Study MOD-020 was an open label pharmacokinetics and safety study in twelve permanently hospitalized, elderly subjects with "deficit psychological-pathological symptoms" performed in France. Modafinil was administered at 300 mg in the a.m. on Days 1 and 7, and 150 mg bid on Days 2 through 6. *Of note in this study,  $C_{max}$  measured on Day 1 was almost double that recorded in healthy young volunteers in Study MOD-018.* All twelve patients experienced AE's, the most common being: restlessness, sleeplessness and anxiety. One subject withdrew because of insomnia, nervous irritation, brusque movements, and feeling emotional. There were no SAE's. Reportedly these AE's decreased over time during the study.

In general, there were no consistent or significant qualitative differences between the different age groups in the body system categories of AE's, SAE's, or related SAE's reported.

**SECTION 8.4.4 ADVERSE EVENTS BY RACE:**

Information regarding race was obtained only from the Cephalon sponsored studies. In the Phase 3 studies, the percentages of Black, White or Other subjects reporting AE's were similar in the modafinil and placebo groups, with the exception of Other subjects in the placebo group who had a lower percentage of subjects reporting AE's. However, this group was represented by a small number of subjects. The percentages of subjects reporting SAE's or SAE's related to study drug were also comparable in the three groups.

A higher percentage of Black subjects in the modafinil group (89%) reported AE's compared to White subjects (72%) or Other subjects (67%) in the Phase 1/2 studies. Of note, 55% of Black subjects in the placebo group reported AE's compared to 19% of White subjects; no Other subjects received placebo. The sponsor suggests that this finding is due to the fact that many of the Black subjects were from Study C1538a/201/AB/US, a study of the abuse potential of modafinil in known substance abusers. This study maximized the AE profile of modafinil by employing doses as high as 800 mg/d and by eliciting reports of AE's via questionnaires.

In general, there were no consistent or significant qualitative differences between the different racial groups in the body system categories of AE's, SAE's or related SAE's reported.

#### **SECTION 8.4.5 ADVERSE EVENTS IN PATIENTS WITH HEPATIC INSUFFICIENCY:**

Nine subjects with severe hepatic insufficiency due to cirrhosis were studied in the foreign trial MOD-021. They received modafinil 200 mg/d for eight days. Plasma levels of modafinil were higher in these subjects compared to healthy subjects tested in Study MOD-019. One subject died during the study due to worsening of encephalopathy. This event was judged not to be related to modafinil. There were no other SAE's reported. There was a significant increase in mean prothrombin level in one subject and there were significant increases in blood urea levels in two others. These abnormalities were judged not to be related to modafinil administration.

#### **SECTION 8.4.6 ADVERSE EVENTS IN PATIENTS WITH RENAL INSUFFICIENCY:**

Ten male subjects with severe chronic renal failure who were not receiving dialysis were studied in the foreign Study P1595. They received a single 200 mg dose of modafinil following an overnight fast. The pharmacokinetic profile of modafinil in chronic renal failure patients was reportedly similar to that seen in healthy subjects in Study MOD-022, with the exception that there was an increase in the plasma concentration of the acid metabolite. The sponsor reports that there were no SAE's and no clinically significant alteration in laboratory or clinical safety parameters in this patient group.

#### **SECTION 8.4.7 ADVERSE EVENTS RELATED PREGNANCY, NURSING, LABOR AND DELIVERY:**

No human studies were conducted specifically to evaluate the effects of modafinil on female reproductive function. There were seven normal births which occurred in patients who received modafinil during pregnancy. One subject (#2009) in Study C1538a/302/NA/US was treated for approximately two months with modafinil 400 mg/d when she developed abdominal pain and vaginal bleeding and had a positive pregnancy test. Just over a month later she had a spontaneous abortion. This was her third spontaneous abortion.

The sponsor reports that there were no reports of patterns of AE's that indicated that modafinil adversely affected the menstrual cycle, fertility, or the normal course of pregnancy or lactation. However, they do note that the potential for modafinil to cause induction of liver enzymes at doses of 400 mg/d or higher, may result in decreased efficacy of minidose estrogenic hormonal contraceptives.

**SECTION 8.5****OTHER SAFETY FINDINGS:****SECTION 8.5.1****CLINICAL LABORATORY EVALUATIONS:**

The laboratory data base consists of results from all Cephalon sponsored studies. Laboratory data were obtained intermittently in the foreign, non-Cephalon studies; the sponsor chose not to include those results in the data base.

The criteria for identifying laboratory values of clinical concern are defined in the sponsor's Table Following Text 25.0.0, Item 8, Vol. 5, pp. 02000-02002. A copy of that table is included as Appendix II of this review.

**Section 8.5.1.1 Clinical Chemistry:**

The sponsor reports that there were no treatment emergent, clinically significant changes in mean plasma levels of liver function tests (ALT, AST, GGT, total bilirubin) in the double blind or open label extension periods of the pivotal studies. Examination of the sponsor's Tables Following Text 21.1.1 through 21.1.5 (Item 8, Vol. 5, pp. 02003-02048) reveals that a small number of subjects did have significant elevations of these liver function tests. However, for ALT, AST and total bilirubin, the numbers of subjects with abnormalities is higher in the placebo group (where available) for all study subsets except the Cephalon Phase 1/2 subset which had no placebo treated subjects with abnormal bilirubin results and 2 (2.3%) modafinil treated subjects with abnormal bilirubin results. In the open label extension trials there were 4 (0.9%) subjects with significantly elevated ALT levels, 5 (1.1%) subjects with significantly elevated AST levels, and 1(0.2%) subject with significantly elevated total bilirubin levels.

Plasma levels of GGT did show dose dependent, treatment emergent increases in modafinil treated subjects from baseline through Week 9 in the double blind portions of the studies and in the open label extensions. There were 4 (1.1%) modafinil treated subjects and 1 (0.5%) placebo treated subject in the two pivotal studies who developed significant elevations of GGT. In the open label extension studies, there were 11 (2.4%) subjects who had significant elevations of GGT. Of all subjects with any elevation of GGT in the double blind Cephalon studies, 7 (5%) occurred in the placebo group, 6 (4%) in the 200 mg/d modafinil group, and 16 (10%) in the 400 mg/d modafinil group. It should be noted, however, that none of the GGT elevations were markedly high, a number of the subjects had elevation at screening or baseline, some had other causes likely to explain the elevation (medical history, current medical problem, and/or concomitant medications), and a number of subjects showed decreasing values when they remained on study drug.

In the Phase 1/2 trials there was a higher percentage of subjects with significantly abnormal bicarbonate levels in the modafinil compared to the placebo group (5/66, 5% vs. 0/20, 0%, respectively). In these studies, 5 modafinil treated subjects had bicarbonate levels shift (of any degree) from normal to high and 14 modafinil treated subjects had a shift from normal to low.

Clinically significant abnormal chemistry values for the modafinil and placebo treatment

groups, by study type subset, are summarized in the sponsor's Table 8.9-23, "Frequencies of Treatment-Emergent, Clinically Significant Abnormal Clinical Chemistry Values." (Item 8, Vol. 3, p. 01048), reproduced below:

**Table 40. Clinically Significant Abnormal Clinical Chemistry Results**

Laboratory Parameter	Subjects with a Specific Laboratory Abnormality Number Abnormal/Number Assessed (%)			
	Cephalon Phase 3 Double-Blind		Cephalon Phase 1/2	
	Modafinil	Placebo	Modafinil	Placebo
Albumin	0/356 (0)	0/182 (0)	0/110 (0)	0/20 (0)
Alkaline Phosphatase	0/356 (0)	0/182 (0)	0/110 (0)	0/20 (0)
ALT	0/356 (0)	1/182 (1)	0/110 (0)	0/20 (0)
AST	1/356 (<1)	4/182 (2)	0/110 (0)	0/20 (0)
Bicarbonate	14/356 (4)	7/182 (4)	5/66 (8)	0/20 (0)
BUN	1/356 (<1)	3/182 (2)	0/110 (0)	0/20 (0)
Calcium	9/356 (3)	7/182 (4)	1/110 (1)	0/20 (0)
Chloride	0/356 (0)	0/182 (0)	0/110 (0)	0/20 (0)
Cholesterol	1/356 (<1)	0/182 (0)	0/66 (0)	0/20 (0)
Creatinine	0/356 (0)	1/182 (1)	0/110 (0)	0/20 (0)
GGT	4/356 (1)	1/182 (1)	0/104 (0)	0/18 (0)
Glucose	17/356 (5)	13/182 (7)	1/110 (1)	0/20 (0)
LDH	NR	NR	0/36 (0)	0/12 (0)
Phosphorus	0/356 (0)	0/182 (0)	0/104 (0)	0/20 (0)
Potassium	4/356 (1)	1/182 (1)	1/110 (1)	0/20 (0)
Sodium	1/356 (<1)	0/182 (0)	0/110 (0)	0/20 (0)
Total Bilirubin	0/356 (0)	1/182 (1)	2/86 (2)	0/12 (0)
Total Protein	0/356 (0)	0/182 (0)	0/110 (0)	0/20 (0)
Uric Acid	0/356 (0)	1/182 (1)	0/66 (0)	0/18 (0)

Source: Tables Following Text 26.1.1, 26.1.2, and 26.1.3.

Abbreviations:

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; NR = not recorded.

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### Section 8.5.1.2 Hematology:

There only hematology parameters for which abnormal values occurred more often in the modafinil treated subjects compared to the placebo treated subjects were eosinophil and monocyte counts. This finding only occurred in the Cephalon Phase 1/2 studies. There were no related clinical AE's. While cases of mild to moderate neutropenia was noted, in the double blind studies the incidence of neutropenia (< 1000 absolute neutrophil count) occurred with equal frequency in the modafinil and placebo treatment groups. There were also no reported cases of associated clinical AE's or progressive neutropenia. Examination of the sponsor's Tables Following Text 26.2.1 through 26.2.5 (Item 8, Vol. 5, pp. 02049-02076) confirms these findings.

Clinically significant abnormal hematology values for the modafinil and placebo treatment groups, by study type subset, are summarized in the sponsor's Table 8.9-24, "Frequencies of Treatment-Emergent, Clinically Significant Abnormal Hematology Values." (Item 8, Vol. 3, p. 01051), reproduced below:

**Table 41. Clinically Significant Abnormal Hematology Results**

Laboratory Parameter	Frequency of Specific Laboratory Abnormality Number Abnormal/Number Assessed (%)			
	Cephalon Phase 3 Double-Blind		Cephalon Phase 1/2	
	Modafinil	Placebo	Modafinil	Placebo
APTT	NR	NR	0/36 (0)	0/12 (0)
Bands	0/6 (0)	0/2 (0)	0/1 (0)	0/0 (0)
Basophils	0/356 (0)	0/182 (0)	0/104 (0)	0/20 (0)
Eosinophils	11/356 (3)	8/182 (4)	3/104 (3)	0/20 (0)
Hematocrit	4/356 (1)	0/182 (0)	0/98 (0)	0/18 (0)
Hemoglobin	0/356 (0)	1/182 (1)	0/98 (0)	0/18 (0)
Lymphocytes	14/356 (4)	5/182 (3)	1/104 (1)	0/20 (0)
Monocytes	2/356 (1)	0/182 (0)	4/104 (4)	0/20 (0)
Neutrophils	1/356 (<1)	0/182 (0)	0/104 (0)	0/20 (0)
Platelet Count	0/356 (0)	0/182 (0)	0/104 (0)	0/20 (0)
PT	NR	NR	0/36 (0)	0/12 (0)
RBC	2/356 (1)	0/182 (0)	0/98 (0)	0/18 (0)
WBC	5/356 (1)	0/182 (0)	0/104 (0)	0/20 (0)

Source: Tables Following Text 26.2.1, 26.2.2, and 26.2.3.

**Abbreviations:**

APTT = activated partial thromboplastin time; NR = not recorded; PT = prothrombin time; RBC = red blood cell count; WBC = white blood cell count.

### Section 8.5.1.3 Urinalysis:

The sponsor states that there were no notable differences between modafinil treated and placebo treated subjects in urinalysis tests with treatment emergent, clinically significant, abnormal values. Review of the sponsor's Tables Following Text 26.3.1 through 26.3.5 (Item 8, Vol. 5, pp. 02077-02100) reveals that there was a higher incidence of blood in the urine in the modafinil treated patients vs. the placebo treated patients (27/357, 7.6% and 7/182, 3.8%, respectively) in the double blind studies. However, these findings were transient and nearly all occurred in the female patients.

### SECTION 8.5.2 VITAL SIGNS:

Vital signs data were available only for the Cephalon Phase 3 studies and for ten Cephalon Phase 1/2 studies. The normal ranges used were:

Temperature	less than 101° F
Systolic blood pressure	90 to 180 mm Hg
Diastolic blood pressure	50 to 105 mm Hg
Pulse	50 to 120 bpm

Clinically important shifts from the normal range were:

Temperature	2° increase
Systolic blood pressure	30 mm Hg decrease or 40 mm Hg increase
Diastolic blood pressure	20 mm Hg decrease or 30 mm Hg increase
Pulse	20 bpm decrease or 30 bpm increase

No consistent patterns of change were noted. Although occasional episodes of clinically significant tachycardia did occur during treatment, review of the sponsor's Tables Following Text 28.1.0 through 31.4.0 (Item 8, Vol. 6, pp. 02244-02518) confirm that these episodes do not occur with any greater frequency in the treatment groups compared to the placebo groups of the double blind studies.

### SECTION 8.5.3 BODY WEIGHT:

There was no difference between the modafinil treated and placebo treated subjects with a clinically significant change from Baseline in body weight ( $\pm 7\%$ ). A significant weight loss was observed in 6 (2%) modafinil treated subjects and in 2 (1%) placebo treated subjects. A significant increase in body weight was observed in 5 (1%) modafinil treated subjects and 7 (4%) placebo treated subjects.

### SECTION 8.5.4 ECG

Treatment emergent ECG abnormalities were observed in 125/404 (31%) of modafinil treated and 48/140 (34%) of placebo treated subjects who were normal at baseline. The sponsor reports that no treatment emergent patterns of abnormalities were noted.

**SECTION 8.6**            **DOSE-RESPONSE ADVERSE EXPERIENCE INFORMATION:**

The sponsor reports that in the Cephalon sponsored Phase 3 studies there was a slightly higher incidence of AE's at the 400 mg/d dose compared to the 200 mg/d dose in the body system categories for which AE's were most frequently reported, i.e. nervous system, body as a whole, and digestive system. There was only one AE, headache, for which the difference in incidence was > 5%.

**SECTION 8.7**            **DRUG-DRUG INTERACTIONS:**

**SECTION 8.7.1**            **INTERACTION WITH CLOMIPRAMINE:**

Study C1538a/107/PK/UK, a Cephalon sponsored study performed in the U.K., examined the pharmacokinetics and safety of coadministration of modafinil and clomipramine in 18 normal, healthy subjects. This study was undertaken because clomipramine is often used in subjects with narcolepsy for the treatment of cataplexy. Combined treatment with clomipramine 50 mg/d and modafinil 200 mg/d did not affect the pharmacokinetics of either drug. There were no deaths or SAE's. There were a total of 75 reported AE's; 37 of which occurred with clomipramine alone, and 27 of which occurred with combined treatment. There were no clinically significant changes in ECG, clinical chemistry, hematology or urinalysis parameters. In subjects receiving combined treatment, the sponsor reports a significantly greater increase in systolic blood pressure than occurred with either treatment alone (12.4 mm Hg for combined treatment; 6.4 mm Hg for modafinil alone; 5.7 mm Hg for clomipramine alone).

**SECTION 8.7.2**            **INTERACTION WITH METHYLPHENIDATE:**

Study C1538a/109/PK/UK, a Cephalon sponsored study performed in the U.K., examined the pharmacokinetics and safety of coadministration of modafinil and methylphenidate in 22 normal, healthy subjects. Combined treatment with methylphenidate 40 mg/d and modafinil 200 mg /d resulted in statistically significant increases in mean  $t_{max}$  for modafinil ( $1.9 \pm 0.8$  hr versus  $2.9 \pm 0.9$  hr) and modafinil acid ( $2.8 \pm 0.9$  hr versus  $3.6 \pm 1.3$  hr) compared to modafinil treatment alone. There were no deaths or SAE's. No clinically significant changes in safety parameters were observed.

**SECTION 8.7.3**            **INTERACTION WITH TRIAZOLAM:**

Study MOD-016, a non-Cephalon study performed in France, examined the effect on memory and psychomotor performance, as well as safety, of coadministration of modafinil and triazolam in 12 normal, healthy subjects. Triazolam was chosen because narcolepsy patients are at times treated with this drug for nighttime insomnia induced by the use of stimulants during the day. A single dose of modafinil 50, 100 or 200 mg administered with triazolam 0.25 mg resulted in no clinically significant alterations in the AE profile of either drug used alone. Clinical laboratory evaluations were not conducted.

#### SECTION 8.7.4 INTERACTION WITH CONCOMITANT MEDICATIONS:

Information regarding AE's in subjects treated concomitantly with modafinil and other medications was obtained from the Cephalon Phase 3 double blind trials. The sponsor's Table 8.9-25, "AEs Occurring in Subjects Treated with Concomitant Medication in Specified Categories in Cephalon Phase 3 Double-Blind Studies" (Item 8, Vol. 3, p. 01061), is reproduced below:

**Table 42. Incidence of AE's in Subjects Treated with Concomitant Medication**

Medication	Subjects Reporting Any AE N (%)		
	Placebo	Modafinil 200 mg/d	Modafinil 400 mg/d
Narcolepsy Medications <sup>1</sup>	4 (57)	4 (67)	8 (89)
Other Stimulants <sup>2</sup>	11 (100)	13 (93)	11 (100)
Sedatives <sup>3</sup>	28 (93)	22 (92)	34 (94)
Hormones <sup>4</sup>	33 (83)	26 (87)	32 (100)

<sup>1</sup> Includes dexamphetamine, caffeine, desipramine, pemoline, protryptiline, and imipramine.

<sup>2</sup> Predominantly cold and sinus preparations (e.g., pseudoephedrine).

<sup>3</sup> Predominantly antihistamine preparations, including loratadine, astemizole, chlorpheniramine, diphenhydramine, and terfenadine; also includes diazepam.

<sup>4</sup> Predominantly oral contraceptive preparations, including estradiol, estrogens, and medroxyprogesterone.

The numbers are small making interpretation difficult. However, the sponsor does report that the percentage of subjects who took narcolepsy medications, stimulants, or sedatives, and reported nervous system AE's, was higher for subjects receiving modafinil than for subjects receiving placebo. They cite the following example: 5/9 (56%) patients receiving 400 mg of modafinil who took other narcolepsy medications reported nervous system AE's compared to 2/6 (33%) patients who received 200 mg of modafinil and took other narcolepsy medications and 1/7 (14%) patients who received placebo and took other narcolepsy medications. This occurred on a background of a modafinil dose related trend towards more nervous system AE's for all study subjects.

#### SECTION 8.7.5 POTENTIAL DRUG-DRUG INTERACTIONS:

In the non-Cephalon sponsored Study P1424, doses of modafinil 400 mg/d or more decreased the half-life of antipyrine. Modest reductions of group mean blood levels of modafinil itself were noted over time in patients receiving 400 mg/d, indicating the possibility of autoinduction of metabolism. The dose related elevations of GGT noted in the Cephalon studies also suggests an activation of hepatic metabolism. Autoinduction has been clearly noted in the preclinical studies [see Dr. Atrakchi's review for this NDA].

The human liver cytochrome P450 enzyme CYP2C19, which plays a role in the metabolism of diazepam and propranolol) was significantly inhibited in *in vitro* studies. Modafinil is 61-65% bound to plasma proteins, essentially to albumin. It does not change the binding

characteristics of warfarin, diazepam or propranolol in *in vitro* studies, however.

### SECTION 8.8

#### ADVERSE EFFECTS IN LONG TERM USE:

There were no deaths in the Cephalon open label studies. SAE's were reported in 27/478 (6%) subjects. Information regarding these events has previously been discussed in Section 8.2.2 of this review. For AE's in body systems most frequently reported (body as a whole, digestive, nervous and cardiovascular), the frequency of AE's reported during the first eight weeks of open label dosing was approximately half the frequency of AE's reported during the eleven week double blind dosing periods. The frequency of AE's in these body systems tended to decline further during the subsequent weeks, such that the frequency of AE's reported during open label Weeks 33 through 40 or more was approximately one-fourth to one-half the frequency reported during open label Weeks 1 through 8.

Forty of 478 (8%) subjects discontinued due to AE's in the Cephalon Phase 3 open label studies compared to 5% in the Cephalon 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). The types of 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 nervous system AE's. These AE's included: nervousness (7 subjects), anxiety (4 subjects), depression (3 subjects) and cataplexy (2 subjects).

GGT plasma levels showed a small mean increase during the 40 week open label continuation periods of the Cephalon Phase 3 studies. This appeared to be due to levels that were elevated to a clinically significant extent in just a few subjects. Median GGT levels showed little or no continued elevation. This is confirmed by examination of the sponsor's Tables 27.1.5 and 27.1.6, "Summary of Clinical Chemistry - Mean GGT (+ - 2 S.E.)" and "Summary of Clinical Chemistry - Median GGT (25th, 75th percentile)"; (Item 8, Vol. 6, pp. 02175-02176).

As in the double blind studies, cases of mild to moderate neutropenia were observed. There were, however, no cases of associated symptoms or progressive neutropenia, and treatment with modafinil did not appear to worsen pre-existing cases of benign neutropenia.

In the non-Cephalon Study MOD-026, 56 subjects with narcolepsy or hypersomnia received 100 to 500 mg/d of modafinil initially. The dose was then adjusted at the investigators' discretion and most subjects were maintained on 200 to 300 mg/d. Duration of treatment ranged from one month to three years. Ten subjects received modafinil for one year or longer. Seven subjects withdrew or were discontinued from the study due to AE's. These AE's included: salivation disorders, restless legs, nausea, anxiety, and "internal tension."

In the non-Cephalon Study MOD-028, 319 subjects with narcolepsy (242 subjects), hypersomnia or other diagnoses, received 50 to 600 mg of modafinil per day initially. The dose was then adjusted at the investigators' discretion and most subjects were maintained on 100 to 300 mg/d. Duration of treatment ranged from one month to ten years. Eighty-one subjects received modafinil for one year or greater and 37 subjects received modafinil for three years or greater. Sixty-seven subjects reported a total of 319 AE's. These AE's included:

irritability, sleep disorders, headaches, and gastric pain. Ten subjects withdrew from the trial due to AE's, which included: depression, gastric pain, asthenia, dyspnea, nervousness, cutaneous eruption, anorexia, and "poor tolerance." There were 3 SAE's: myocardial infarction, cranial trauma, and abdominal surgery for stenosis.

**SECTION 8.9**                    **ADVERSE EFFECTS FOLLOWING WITHDRAWAL OF THERAPY:**

The effects of discontinuation from modafinil were assessed in Study C1538a/301/NA/US. In this study, patients were taken off drug during a two week period prior to the open label extension period. The frequency of subjects reporting new AE's was comparable between subjects discontinued from placebo (2 subjects), 200 mg/d modafinil (3 subjects), and 400 mg/d modafinil (2 subjects).

Study C1538a/302/NA/US systematically evaluated the effects of withdrawal from modafinil. Patients who completed the 9 week double blind phase, or who terminated for reasons other than noncompliance or a medication related AE, were given the opportunity to participate in a two week double blind withdrawal phase before entering the open label phase. Patients were randomized to a withdrawal period dose at the beginning of the study: 20% of patients in the 400 mg/d dose group and 20% of patient in the 200 mg/d dose group were randomly assigned to receive modafinil at the same dose (400/400 mg/d and 200/200 mg/d); 80% of the patients were randomly assigned to receive placebo (400/placebo and 200/placebo); and the placebo treated patients remained on placebo (placebo/placebo). A total of 240 patients entered the withdrawal phase:

400/400	10 patients
400/placebo	71 patients
200/200	9 patients
200/placebo	69 patients
placebo/placebo	81 patients

Although there was an indication of slight worsening excessive daytime sleepiness, based on MWT results, for patients withdrawing from either dose of study drug, the AE 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 evidence of an amphetamine type withdrawal syndrome.

In non-Cephalon Study 917, Parkinson's disease patients treated with 200 or 300 mg/d of modafinil for 21 days experienced no withdrawal symptoms during a seven day observation period. In non-Cephalon Study P1424, 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 related to withdrawal noted by the investigator was drowsiness occurring in 7/8 patients who completed dosing in the 1000 mg/d group.

APPEARS THIS WAY ON ORIGINAL