

Table 1
Summary of Exposure to Modafinil in Cephalon-sponsored and Non-Cephalon-sponsored Studies

	Average Daily Dose	Duration of Exposure					Total	
		≤14d	14-28d	29-90d	91-179d	180-364d		≥ 365d
Cephalon-sponsored studies (Phase 1, 2, 3; DB and OL)	< 175 mg	1	0	2	0	3	6	12
	175-224 mg	135 [†]	8	21	5	15	20	204
	225-374 mg	0	3	17	26	118	184	348
	375-424 mg	29	18	21	19	31	12	130
	≥ 425 mg	62 [‡]	4	0	0	0	0	66
Foreign (non-Cephalon-sponsored) studies [‡]	< 175 mg	77	26	38	4	2	30	177
	175-224 mg	0	1	0	0	0	0	1
	225-374 mg	261	76	53	25	40	90	645
	375-424 mg	61	89	156	26	47	86	465
	≥ 425 mg	175	47	19	9	4	42	296
	Unknown	3	0	2	2	0	7	14
Total		805	272	329	116	260	477	2258

† Subject counts include a single subject (counted only once) who participated in two Cephalon-sponsored studies and was exposed to modafinil 800 mg for six days in protocol 102 (subject number 23) and to modafinil 200 mg for 1 day in protocol 103 (subject number 102) for seven days of exposure at an average daily dose of 714 mg.

‡ Subject counts do not include 77 (15 + 62) exposures to modafinil for which insufficient information was available on CRF to unambiguously establish patient identity.

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III. Conclusions

Based upon our thorough review of all 1704 CRFs from subjects exposed to modafinil in 81 non-Cephalon-sponsored studies, we have determined that at least 1505 unique, identifiable subjects were exposed to modafinil in these studies. Adding to this the 760 unique subjects exposed to modafinil in Cephalon-sponsored studies, a total of 2265 subjects have been exposed to modafinil worldwide; 737 for 180 days or longer and 477 for 365 days or longer.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL SAFETY REVIEW OF NDA RESUBMISSION

Brand Name: Provigil
Generic Name: Modafanil
Sponsor: Cephalon
Indication: Narcolepsy
NDA Number: 20-217
Original Receipt Date: 6/30 98
Clinical Reviewers: Joel Freiman, M.D.
Review Completed: 12/16/98

SECTION 8.0 SAFETY FINDINGS

SECTION 8.1 METHODS

This review of the safety of modafanil in the exposed population is centered on the information provided by the sponsor in the Integrated Summary of Safety Update (NDA 20-717 Resubmission June 30, 1998, Vol. 19) and a Response to FDA Request for Information, December 14, 1988. This update reviews safety from the following sources:

- 1) OPEN-LABEL PHASE 3 CLINICAL TRIALS (C1538a/301/NA/US and C153a/302/NA/US combined; open-label and first extension)
- 2) C1538a/201/AB/US (12 female subjects in phase B)
- 3) C1538a/112PK/UK (26 male subjects)

Other Sources of Safety Information: UK and Ireland Named Patient Program, Foreign Non-Cephalon-sponsored Study Results, Foreign Marketing Experience

The database cut-off date for the open-label and extensions of protocols 301 and 302 is June 2, 1997. Additional information from all sources on deaths, discontinuations due to adverse experiences, and serious adverse experiences are provided through January 31,

1998 from non-queried case report forms. A teleconference was conducted with the sponsor on November 17, 1998. The sponsor clarified the term 'non-queried' to mean that there is a complete accounting for all deaths, discontinuations and serious adverse experiences through January 31, 1998, however, complete verification and entry into the sponsor's electronic database has not yet been completed.

Narrative summaries of new deaths and new adverse events leading to discontinuation were reviewed. Many of the tabular summaries were examined in their entirety.

SECTION 8.2.SERIOUS ADVERSE EVENTS:

SECTION 8.2.1 DEATHS:

One death occurred during extended open-label treatment in Study 302 (pat #1904). A 38-year old man, who was receiving 400 mg/day of modafanil, died of a broken neck as a result of a snowmobile accident. This accident was assessed by the investigator as being possibly related to study medication. The sponsor provided the following explanation as to why the investigator attributed this death as possibly related to study drug (teleconference Nov. 17). At the time that the investigator was informed of the death, the investigator was not aware that a snowmobiling accident had occurred, only that the patient had died.

No deaths were reported among subjects in study 201.

No deaths were reported among subjects in study 112.

SECTION 8.2.2 NON-FATAL SERIOUS ADVERSE EVENTS:

Fifty subjects reported SAE's in open-label phase 3 clinical trials 301 and 302. Twenty-seven represent previously unreported adverse experiences. Among the 27 previously unreported SAE's 12 occurred after the database cutoff date. Each subject who had a serious adverse experience is listed in Vol. 19, Table 9, pp. 46-48 (Attachment 1). None of the experiences were considered probably related or related to study drug. There was no discernible pattern to the adverse experiences. Patient narratives are not provided for subjects with SAE's that did not also discontinue study medication.

No serious or potentially serious adverse experiences were reported among subjects in study 201.

No serious adverse experiences were reported among subjects in study 112.

SECTION 8.3 ASSESSMENT OF DROPOUTS:

SECTION 8.3.1 MODAFANIL EXPOSURE

A total of 478 eligible patients entered the initial 40-week open-label phase of studies 301 and 302. Those who completed the 40-week phase had the option of continuing in the 48-week open-label extension phase. Further extensions were offered, however only the 40-week and 48-week phase results are presented.

A total of 209 patients had reached open-label extension week-48 by the data cut-off date. Overall, 13% of patients discontinued due to lack of study medication efficacy, 10% of patients discontinued due to adverse experiences. A complete accounting of patient disposition is presented in Vol. 19, Table 1, p. 33 (Attachment 2).

Overall treatment exposure by average daily dose is presented in Vol. 19, Table 2, p. 34 (Attachment 3). Among the 478 patients studied the mean modafanil exposure was 419 days, with an average dose of 305 mg/day, (Vol. 19, Table 3, p 35).

A total of 12 women with histories of polysubstance abuse received one dose each of placebo, methylphenidate 45 mg and 90 mg, and modafanil 200 mg, 400 mg and 800 mg in study 201.

A total of 26 healthy men were enrolled in study 112 to examine the single-dose pharmacokinetics of modafanil 200 mg, and dexamphetamine 10 mg when given alone or in combination.

SECTION 8.3.2 NEW ADVERSE EXPERIENCES RESULTING IN PATIENT DISCONTINUATION

The sponsor's Vol. 19, Table 8, pp. 42-44 (Attachment 4) presents a summary of adverse experiences leading to discontinuation in open-label studies 301 and 302. New adverse experiences that resulted in discontinuation from study that were not previously reported in the double-blind or open-label phases of 301 and 302 include the following:

- 1) Anemia, endometrial carcinoma, leukopenia with liver enzyme elevations, mood change, pruritis, somnolence and goiter occurred in one patient each.
- 2) Congestive heart failure and cardiomegaly occurred in the same patient.
- 3) Four unintended pregnancies; one patient used oral contraceptives alone, one patient used barrier method alone, one patient used both barrier and oral contraceptive methods, and one patient discontinued medroxyprogesterone acetate injections 502 days prior to becoming aware that she was pregnant.
- 4) Two patients experienced an increase in cataplexy

Review of the narrative summaries did not reveal any to be clearly related to the study drug with the exception of the patient who became pregnant while on oral contraceptives alone. Proposed modafanil labeling notes that the effectiveness of steroidal

contraceptives may be reduced with modafanil. The patient with elevated liver enzymes and leukopenia was judged by the investigator to be possibly related to modafanil and this case is presented in greater detail.

A 39-year old (patient number 1202) had been diagnosed with narcolepsy for 1 year. In the double-blind phase he received placebo. In the open-label phase he received modafanil 100 or 200 mg/day for 373 days. His only concomitant medication was ASA. Beginning on day 290 the patient was noted to have the following liver enzyme and hematologic abnormalities ALT 214 IU/L, AST 124 IU/L, GGT 100 IU/L, WBC 8.3 (37.9% neutrophils and 49.4 % lymphocytes). The patient last received study medication on day 373 because of persistent abnormalities and was discontinued from the study on day 388. The patient was seen in consultation by a hematologist on 3/19/96 and again 3/25/96. The consultation note stated that the patient reported no history of alcohol abuse or any history of exposure to risk factors for viral hepatitis. The patient was felt to have a relative lymphocytosis, and elevated liver enzymes which could be explained by the medication. No further follow-up is provided.

SELECTED LFT'S (PATIENT 1202)

DATE	AST (IU/L) Ref. (6-37)	ALT (IU/L) Ref. (8-48)	GGT (IU/L) Ref. (7-64)	Alk.Phos(IU/L) Ref. (31-121)
2/11/95 OL baseline	56	80	35	60
11/30/95 day 290	124	214	100	67

2/13/96 day 365	132	298	167	61
3/7/96 day 388	146	305	85	60

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SELECTED HEMATOLOGY (PATIENT 1202)

DATE	WBC (X10E3/UL) Ref. (4.1-12.3)	Neutrophils (%) Ref. (40.9 – 77%)	Lymphs (%) Ref. (15.5 – 46.6%)
2/11/95	10.5	55.7	29.8
11/30/95	8.3	37.9	49.4
2/13/96	10.9	28.6	58.4
3/7/96	9.4	30.0	61.0

No subjects discontinued from study 201 due to adverse experience.

One subject in study 112 discontinued due to syncope. This event occurred at visit one upon intravenous cannulation prior to the administration of any study drug.

SECTION 8.4 OTHER ADVERSE EVENTS

Open-label emergent adverse experiences that were experienced by at least 5% of the safety population in any dosage group are summarized by the sponsor in Vol. 19, Table 6, p. 38 (Attachment 5). Most open-label emergent experiences did not appear to be dose-related. Mild to moderate headache was the most common adverse experience.

Open-label adverse experiences that were drug related are presented in Vol. 19, Table 7, p. 40 (Attachment 6). Drug-related adverse experiences were greatest for the 200 mg/day

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group, 45% verses 8% and 19% for the 400 mg/day and 300 mg/day groups respectively. Nervousness and anxiety were more frequent in the 200 mg/day group.

The reporting of new adverse experiences decreased across time among all dosage groups (Vol. 19, Table 3.2.0, p. 212).

Among the 12 female subjects in study 201 the majority of adverse experiences were mild to moderate in severity (Vol. 33, Appendix 4.0, Table 9.1B, pp. 4679-4695).

Among the 26 subjects in study 112 the majority of adverse experiences were mild to moderate in severity (Vol. 34, Appendix 5.0, Table 9.1 pp. 5139-5142).

SECTION 8.5 OTHER SAFETY FINDINGS:

SECTION 8.5.1 CLINICAL LABORATORY EVALUATIONS

The laboratory database for studies 301 and 302 consists of values for laboratory tests at baseline, at each of the study visits, and at endpoint.

SECTION 8.5.1.1 CLINICAL CHEMISTRY - Liver

Descriptive statistics and changes from baseline for blood chemistry parameters are summarized in Vol. 19, Tables 4.0.0 and 4.0.1, pp. 289-378 (studies 301 and 302). Shift tables for blood chemistry are found in Vol. 20, Tables 4.0.2, and 4.0.3, pp. 379-420.

No clinically important mean values or changes from baseline in AST, ALT, total protein, albumin, or total bilirubin occurred at any of the visits for any of the treatment groups.

None of the mean alkaline phosphatase values were clinically important at any visit. However alkaline phosphatase showed gradual increases from baseline through week 88 in a dose dependent manner (Vol. 19, Table 10, p. 50).

None of the mean GGT values were clinically important at any visit. However, GGT showed gradual increases from baseline at each visit in a dose dependent manner (Vol. 19, Table 11,9 p. 51, and Attachment 7). While none of the mean values were clinically significant at any visit, twelve subjects had clinically significant values (Vol. 23, Listing 4.0.0, pp. 1318-1438).

At the request of the FDA the sponsor has provided additional information on patients in which the GGT test was clinically significantly elevated. This additional information is contained in a Response to FDA Request for Information dated December 14, 1998.

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Among the 12 patients with clinically significant elevations of GGT, 7 patients experienced transient elevations which either normalized completely (2 patients) or partially normalized (5 patients). These seven complete or partial resolutions occurred in the setting of continued treatment (3 patients), discontinuation of treatment (2 patients), and dose reduction (2 patients). None of the patients with clinically significant elevations of GGT had concomitant clinically significant elevations of total bilirubin.

Among the 12 patients with clinically significant elevations of GGT, 5 patients still had clinically significant elevations at endpoint. Endpoint refers to the last reported value in the 6/2/97 database.

Two patients (301/1306; 301/1719), experienced non progressive clinically significant open-label endpoint elevations in the setting of clinically significant GGT elevation at double-blind baseline (patient 1306 baseline GGT 182 IU/L, open-label day 677 GGT 239 IU/L; patient 1719 baseline GGT 230 IU/L, open-label day 633 212 IU/L). Both of these patients remained on modafanil 300 mg/day during open-label treatment.

Two patients (301/2114; 302/1505) experienced resolving clinically significant elevations of GGT in the setting of elevated GGT at double-blind baseline. Patient 2114, a 36 year-old woman, had a double-blind baseline GGT of 151 IU/L. During treatment with modafanil 400 mg/day the maximal GGT was 464 IU/L at day 66. During open-label treatment (modafanil 400 mg/day), clinically significant elevations of GGT persisted to a maximum value of 447 IU/L at open-label day 109. In the setting of continued treatment

with dosage reduction the last reported GGT was 267 IU/L on day 267. The patient did not elect to continue further open-label treatment. Patient 1505, a 60 year-old woman had a double-blind baseline GGT of 152 IU/L. During the double-blind treatment (modafanil 400 mg/day) the patient had persistent though stable GGT elevations. During open-label treatment (modafanil 300 mg/day) the maximal GGT value was 360 IU/L at day 286. At the endpoint observation (open-label day 628) the GGT was 267 IU/L occurring in the setting of dose reduction and discontinuation.

One patient experienced a new-onset elevation off GGT to a maximum value of 259 IU/L at open label treatment day 115.

Among subjects in study 201 no clinically significant values are noted during the treatment period (Vol. 33, Appendix 4, Table 11.2B, pp. 4729-4760).

Among subjects in study 112, no clinically significant values are noted during the treatment period (Vol. 34, Appendix 5.0, Listing 7.3 pp. 5010-5035).

SECTION 8.5.1.2 CLINICAL CHEMISTRY - Kidney

Among subjects in studies 301 and 302, no clinically important mean values or changes from baseline in kidney function tests (BUN, creatinine, uric acid) occurred at any of the visits.

There were no clinically meaningful trends in the number of patients with shifts to values above ULN for kidney function tests.

There was no pattern of increased frequency across study weeks, or apparent dose-related effects of the number of patients with clinically significantly abnormal values for BUN, creatinine, and uric acid (Vol. 20, Table 4.0.3, pp. 408-420).

Among 12 subjects in study 201 no clinically significant values are noted during the treatment period (Vol. 33, Appendix 4, Table 11.2B, pp. 4729-4760).

Among subjects in study 112, no clinically significant values are noted during the treatment period (Vol. 34, Appendix 5.0, Listing 7.3 pp. 5010-5035).

SECTION 8.5.1.3 CLINICAL CHEMISTRY – Electrolytes

Among subjects in studies 301 and 302, no clinically important mean values or changes from baseline in any of the electrolyte tests, or cholesterol and glucose occurred at any of the visits or any of the mean dose groups.

No clinically meaningful trends were apparent in the percentage of patients with shifts to values outside the normal limits for chloride, potassium, sodium, bicarbonate, calcium, phosphorus, or cholesterol and glucose.

There was no pattern of increased frequency across study weeks, or apparent dose-related effects in the number of patients with clinically significantly abnormal values for chloride, potassium, sodium, bicarbonate, calcium, phosphorus, or cholesterol and glucose (Vol. 20, Table 4.0.3, pp. 408-420).

Among 12 female subjects in study 201 no clinically significant values are noted during the treatment period (Vol. 33, Appendix 4, Table 11.2B, pp. 4729-4760).

Among subjects in study 112, no clinically significant values are noted during the treatment period (Vol. 34, Appendix 5.0, Listing 7.3 pp. 5010-5035).

SECTION 8.5.1.4 CLINICAL CHEMISTRY – Hematology

Descriptive statistics and changes from baseline for hematology parameters are summarized in Vol. 20, Tables 4.1.0 and 4.1.1, pp. 421-470 (studies 301 and 302). Shift tables for hematology values are summarized in Vol. 20, Table 4.1.3, pp. 487-493).

No Clinically important mean values or consistent increases or decreases in WBC count, eosinophils, monocytes, or basophils occurred at any of the visits for any of the mean groups.

None of the mean lymphocyte or neutrophil percentages were clinically important at any visit.

No clinically important trends were apparent in the mean percentage of patients with shifts to values above or below the normal limits for WBC count or the percentages of neutrophils, lymphocytes, monocytes, basophils, or eosinophils.

There was no pattern of increased frequency across study weeks, or apparent dose-related effects in the number of patients with clinically significant abnormal values for hemoglobin, hematocrit, red blood cell count, white blood cell count, or the percent neutrophils, lymphocytes, eosinophils and basophils.

Among 12 female subjects in study 201, two subjects had clinically significant monocyte counts of 17 and 15 percent (Vol. 19, Table 18, p. 63)

Among 26 subjects in study 112, fifteen subjects had low lymphocyte counts during one or more treatment periods (Vol. 34, Appendix 5.0, Listing 7.2, pp. 4984-5009).

SECTION 8.5.1.5 CLINICAL CHEMISTRY – Urinalysis

Descriptive statistics and changes from baseline for urinalysis parameters are summarized in Vol. 20, Tables 4.2.0.A, 4.2.0B, and 4.2.1, pp. 494-520. Shift Tables for urinalysis are found in Vol. 20, Table 4.2.2 and clinically significantly abnormal values are summarized in Table 4.2.3.

Among 12 female subjects in study 201, no clinically significant values are noted during the treatment period (Vol. 33, Appendix 4, Table 11.3B, pp. 4761-4786).

Among 26 male subjects in study 112, no clinically significant values are noted. Results of screening urinalysis and urine pH at visits 1, 2, and 3 are presented in Vol. 34, Appendix 5.0, Listings 7.4 and 7.5 respectively.

SECTION 8.5.2 VITAL SIGNS:

SECTION 8.5.2.1 VITAL SIGNS – Blood Pressure

Among subjects in studies 301 and 302, no clinically important mean values or mean changes from baseline in any of the blood pressure measurements occurred at any of the visits.

There were no clinically meaningful trends in the number of patients with clinically significant blood pressure measurements (Vol. 20, Table 5.0.0).

Among 12 female subjects in study 201, both methylphenadate and modafanil produced increases compared to placebo in supine and standing systolic and diastolic blood pressure as evidenced by increases in the AUC for change from 0 to 6 hours and maximum response within 6 hours of dosing (Vol. 33, Appendix 4.0, Tables 8.3.1B, 8.4.1B, 8.7.1, and 8.8.1B). Graphical presentations of mean changes in blood pressure

are presented in Appendix 4.0, Figures 3.3B, 3.4B, 3.7B, and 3.8B. These blood pressure increases were not clinically meaningful.

Among 26 subjects in study 112, small increases in systolic and diastolic blood pressure were observed following administration of all three treatments (Appendix 5.0, Graphs 1, and 2).

SECTION 8.5.2.2 VITAL SIGNS – Pulse

Among subjects in studies 301 and 302, no clinically important mean values or mean changes from baseline in any of the pulse or body temperature measurements occurred at any of the visits

There were no clinically meaningful trends in the number of patients with clinically significant pulse or body temperature measurements (Vol. 20, Table 5.0.0).

Among 12 subjects in study 201, increases in the AUC of the change in standing and supine pulse rate compared to placebo were observed for all active doses except modafanil 200 mg (Vol. 33, Appendix 4.0, Tables 8.5.1B, 8.9.1B and 8.9.2B).

Among 26 subjects in study 112, small increases in pulse were observed following administration of all three treatments (Vol. 34, Appendix 5.0, and Graph 3).

SECTION 8.5.3 BODY WEIGHT:

Among subjects in studies 301 and 302, there were no clinically meaningful mean weight values or mean change for patients. However, average body weight decreased with modafanil treatment by 1 to 3 pounds in a dose-related fashion, from open-label baseline to week 48 across the study period.

There were no clinically meaningful trends in the number of patients with clinically significant body weight changes from open-label baseline (Vol. 20, Table 5.0.0).

SECTION 8.5.4 ECG:

Among subjects in studies 301 and 302, ECG status by visit, including shifts and frequency of clinically significant abnormal values are shown in Vol. 20, Table 6.0.0.

Treatment with modafanil was not systematically associated with clinically meaningful ECG abnormalities. All recorded ECG abnormalities including those judged by the investigator to be not clinically significant were reviewed and no treatment-dependent pattern of abnormalities was found.

No clinically meaningful trends were apparent in the number of patients with shifts from normal to abnormal for ECGs. There were no clinically meaningful trends in the number of patients with clinically significant ECG values (Table 6.0.0).

Among 12 subjects in study 201, no clinically significant changes in ECGs were observed.

Among 26 subjects in study 112, no clinically significant ECG changes were observed (Vol. 34, Appendix 5.0, Listing 5.3, pp. 4932-4956).

9.0 ADDITIONAL STUDIES WITH SAFETY INFORMATION

9.1 Cephalon Named Patient Program in the UK and Ireland

As of 1/31/98 64 patients had started treatment with modafanil, 39 of who were continuing. Ten patients discontinued due to adverse experiences, two (both with worsening cataplexy) of which were serious. No deaths occurred. Patients who discontinued due to an adverse experience are summarized in (Vol. 19, Table 22, p. 73 and Attachment 8). Four of the 10 discontinuations were due to worsening of cataplexy; all were judged possibly or probably related to study drug. Case report forms were not used in this compassionate use program.

9.2 Studies Conducted in Canada

Five studies and one compassionate use program were ongoing or were initiated in Canada since the cut-off date for inclusion in the modafanil NDA-20-717.

9.2.1 Study 94003

No deaths or serious adverse experiences were reported during the conduct of this study. Three patients discontinued due to adverse experiences and are summarized in Vol. 19, Table 23, p. 74, and Attachment 9) Of note a 49 y/o patient taking modafanil 400 mg/day had repetitive movements which were severe and felt probably related to study drug.

9.2.2 Special Access Program

There were no deaths or serious adverse experiences reported during the Canadian compassionate use program. There were nine discontinuations due to adverse experiences which are summarized in Vol. 19, Table 24, p. 75 (Attachment 10). Of note two subjects reported palpitations and a third reported increased leg movements. Case report forms were not consistently used in this compassionate use program and are not provided.

9.2.3 Military Studies in Canada

There were no deaths or serious adverse experiences reported in four Canadian military studies.

9.3 Studies Conducted by [REDACTED]

9.3.1 Discontinuations Due to Adverse Experiences Since NDA Filing

Twenty-two subjects discontinued due to adverse experiences in a series of six studies conducted by [REDACTED] which are summarized in Vol. 19, Table 25, pp. 76-77 (Attachment 11). Two subjects had palpitations one of which also had increased blood

pressure, and a third subject is reported to have had tachycardia. In addition, one subject is reported to have discontinued due to increased facial twitches.

9.3.2 Serious Adverse Experiences Since NDA Filing

Nine subjects had serious adverse experiences in a series of four studies conducted by [REDACTED] which are summarized in Vol. 19, Table 26, p. 78 and Attachment 12).

9.3.3 Serious Adverse Experiences and Discontinuations Due to Adverse Experiences Not Previously Reported in NDA 20-717.

Five subjects with limited presentation in NDA 20-717 are summarized in Vol. 19, Table 27, p. 79 (Attachment 13). Of note one patient each is reported to have experienced one of the following, mannerisms, myoclonic movements, automatisms, and choreiform movements.

Twelve subjects with potentially serious adverse experiences and not presented in NDA 20-717 are summarized in Vol. 19, Table 28, p. 80 (Attachment 14). Only one patient among these twelve patients is known to have discontinued from study due to an adverse experience. A narrative for this patient was reviewed, however narratives are not provided for the patients who did not discontinue from study. Of note one patient each is reported to have experienced one of the following; clonic movements, movement disorder, dyskinesia, extrapyramidal syndrome, and tics.

9.4 Foreign Post-Marketing Experience

Five patients with serious adverse experiences are reported in Vol. 19, Table 29, p. 82 (Attachment 15). Of note, one patient experienced anaphylactic shock on the first treatment day.

9.4.1 Non-Serious Adverse Experiences Reported Outside of Clinical Trials

Forty-nine reports occurring outside of [REDACTED] sponsored clinical trials have been documented. Adverse experiences that were considered possibly related, likely related, or very likely related to modafanil treatment were rash, sweating, pruritis, headache, agitation, anorexia, nervousness, and tachycardia.

Concerns regarding patients with apparent movement disorders were discussed with the sponsor during the November 17, teleconference. The sponsor was aware of these cases and submitted a review of movement disorder adverse events in modafanil clinical trials in a Response to FDA Request for information dated December 14, 1988. A review of the response follows. The review concentrates on the "dyskinesia" adverse events. The incidence of dyskinesia adverse events was 2% in the Cephalon sponsored US 9-week placebo-controlled trials with modafanil.

Methods

The sponsor selected 24 COSTART terms pertaining to movement disorders and searched the NDA ISS and Safety Update to identify patients with one or more of these terms. There was a match for 14 of 24 terms chosen: akathisia, choreoathetosis,

dyskinesia, dystonia, extrapyramidal syndrome, hyperkinesia, hypertonia, hypokinesia, hypotonia, movement disorder, myoclonus, neck rigid, tremor, and twitch.

The sponsor organized the review into the following sections:

- **Serious Adverse Events Associated with “Movement Disorders”**
- **Discontinuations Associated with “Movement Disorders”**
- **Tremor** (verbatim terms such as tremulousness, hand tremors, etc.)
- **Hypertonia** (verbatim terms such as jaw clenching, muscle spasm, etc.)
- **Dyskinesia** (verbatim terms such as dyskinesia bucco-facial, abnormal movements, abrupt movements, involuntary tongue movement, etc.)
- **Hyperkinesia** (verbatim terms such as hyperactivity, restless legs, increased kinetic movement, etc.)
- **Movement Disorders with < 1% Frequency in Modafanil Treated Subjects**
(hypokinesia, neck rigid, twitch, movement disorder, hypotonia, Akathisia, choreoathetosis, myoclonus, dystonia, and extrapyramidal syndrome)

Results

A total of 198 unique subjects among 2277 unique modafanil treated subjects (9%) experienced 250 events related to these terms versus 15 of 521 placebo subjects (3%) who experienced such events.

There were a total of 67 modafanil treated patients who experienced 84 events of tremor.

A total of 39 modafanil treated patients experienced 58 events of hypertonia. A total of

28 modafanil treated patients experienced 29 events of hyperkinesia. There were 43 modafanil treated subjects who experienced 53 movement disorder adverse events.

Serious Adverse Events Associated with "Movement Disorders"

There was 1 "movement disorder" SAE in 1 modafanil treated subject in the Cephalon sponsored (CS) phase 3 trials and 2 movement disorder SAEs in 1 subject in the foreign, non Cephalon sponsored trials (FNC).

The SAE in the CS study involved severe "lower back muscle spasm" in a 60 year-old man related to lifting a lawnmower. The SAE in the FNC involved the accidental overdose (1200 mg of modafanil) in a 15 year-old girl. She experienced 2 dyskinesia SAEs (COSTART verbatim terms "motoric crawling" and "abrupt movements") of unknown severity. She was hospitalized and modafanil treatment discontinued. From the narrative it appears that the SAE resolved after one day.

Discontinuations Associated with "Movement Disorders"

There were 2 movement disorder discontinuations in the CS phase 3 studies and 1 in the CS phase 1-2 studies. One patient in the phase 3 studies experienced moderate muscle tension coded as hypertonia, the other patient experienced mild tremor. A 35 year-old man discontinued from the CS phase 1-2 study while receiving modafanil 400 mg b.i.d on day 9. The patient experienced hyperkinetic movements of the fingers (hyperkinesia), finger tapping, constant chewing motion of the jaw with throat clearing, and "tight body

feeling" (hypertonia). These symptoms lasted 1.5 hours and the patient discontinued modafanil.

There were 12 movement disorder discontinuations in the FNC studies. The events included tremor (2 subjects), akathisia (1 subject), hyperkinesia (4 subjects), dyskinesia (5 subjects).

The 5 modafanil treated subjects who discontinued for adverse event coding to dyskinesia are summarized.

- An 82 year-old man experienced severe abrupt movements on day 2 while receiving modafanil 150 mg b.i.d. All events were continuing at the time of discontinuation.
- A 36 year-old woman with a history of schizophrenia experienced stereotypic movements on day 5 while receiving modafanil 200 mg b.i.d. The AE was ongoing at the time of modafanil discontinuation.
- A 72 year-old man had 2 episodes of bucco-facial dyskinesia while receiving modafanil 300 mg/day. The first episode began at day 54. Modafanil treatment was interrupted for 15 days. The patient had a subsequent episode on after re-starting modafanil (days to onset not provided).
- A 73 year-old woman experienced bucco-facial dyskinesia after three months of modafanil therapy (further information not available).
- A 15 year-old girl experienced motoric crawling and abrupt movements and was previously described.