Dyskinesia

There were 21 modafanil treated subjects who experienced 26 adverse events codiing to dyskinesia. The mean AE onset day was day 100 for the CS phase 3 group, with the onset day not known for the FNC studies. Fourteen of the events were considered to be related to study medication. No change in study medication was made for 15 events. Five subjects previously described discontinued study medication. The dyskinesia resolved without residual in 18 events and in 8 events was ongoing at the time of discontinuation.

Sponsor's Conclusion (dyskinesia)

The sponsor concludes that there does not appear to be an increased risk of developing "tardive dyskinesia" on modafanil. Thirteen of the the dyskinesia AEs in the CS phase 3 studies stopped while the patient was on modafanil or within two weeks of stopping medication. Two subjects are currently still on modafanil despite a dyskinetic AE. Both these AE's are intermittent.

Conclusion10.0

From the available information provided by the sponsor it appears that modafanil treated patients experiencing dyskinesia is related to modafanil. This conclusion is based on the following evidence. There were no reports of dyskinsia adverse events among placebo treated patients. There appears to be a case of dyskinesia with re-challenge (72 year-old man, subject 876/F-04). Two patients experienced dyskinesia within a relatively short time while receiving high doses of modafanil (15 year old girl, subject Open/9-2/K11E; 35 year-old man, subject 102/24) The dyskinesia resolved within a short time of

discontinuing modafanil in these two patients. Two patients remain on modafanil with intermitent dyskinesia, which presumably was not present prior to treatment.

The information available on these cases reviewed by the sponsor is incomplete, especially with respect to factors such as coexisting illnesses, concomitant medications, and outcome, especially in patients from the FNC studies. The sponsor states that thirteen of the dyskinesia adverse events stopped while the subject was on modafanil or within two weeks of stopping medication, however the number in each group is not provided.

As noted by the sponsor, several newly reported adverse experiences and discontinuations indicate the potential for hypersensitivity to modafanil.

As recognized in the initial NDA review of studies 301 and 302, elevations in GGT and alkaline phosphatase continue to show mild elevations over time from baseline in a dose dependent manner. Several cases of clinically significant elevations of GGT were identified. For the most part these patients had elevated GGT at baseline. In most cases there was no associated elevation of AST or ALT. None of the cases were associated with clinically significant elevations of total bilirubin. The clinical significance of these GGT elevations is uncertain.

Several additional cases of tachycardia and hypertension were reported in the update. In addition the pulse and blood pressure measurements from studies 201, and 112 indicate

clinically insignificant increase in pulse and blood pressure following modafanil administration.

Overall, based upon the Integrated Summary of Safety Update, modafanil continues to have a benign safety profile.

/S/

Joel Freiman, M.D.
Medical Reviewer

R. Katz

HFD-120

NDA, 20-217

HFD-120, Freiman, Katz, Hommany

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ATTACHMENT 1

Table 9. Summary of Open-Label Serious Adverse Experiences (C1538a/301/NA/US and C1538a/302/NA/US)

Patient Number	Age	Sex	Adverse Experience[a]	Onset (Study Day)	Severity	Relationship to Study Drug
Modafinil 400 mg/Study 301						
1104	54	M	**Pneumonia**	306	Severe	Remote
1211	60	M	**Joint disorder**	559	Moderate	None
1419	63	M	**Benign tumor in colon and rectum**	871	Severe	None
1423	69	F	**Pneumonia**	831	Severe	None
			Lung cancer	889	Life-threatening	None
Modafinil 400 mg/Study 302						
0302	46	M	**Numbness in bilateral upper and right lower extremities**	895	Moderate	None
0606	37	F	Skin carcinoma*	-20	Mild	None
0913[b]	20	F	**Accidental overdose**	169	NR	NR
1306	50	F	**Endometrial carcinoma**	284	Severe	Remote
1711	51	M	Cerebrovascular accident*	118	Severe	Remote
1804	35	F	Carcinoma*	160	Life Threatening	None
			Brain edema	195	Severe	None
Modafinil 300 mg/Study 301						
0109	27	M	**Bronchopneumonia**[c,d]	722	Moderate	None
0113	54	M	Kidney calculus*	148	Mild	None
0307	51	F	**Wheezing**[c,d]	638	Moderate	Possible
			Palpitations[c,d]	680	Severe	Possible
			Congestive Heart Failure[c,d]	689	Severe	Possible
			Cardiomegaly[c,d]	689	Severe	Possible
0606	28	F	Neoplasia UG* (urogenital)	20	Severe	None
0701	25	M	Intentional injury*	135	Life Threatening	None
0706	48	F	Chest Pain*	125	Severe	Remote
0707	18	M	**Gunshot Wound**[c,d]	741	Mild	None
1307	56	M	Retinal hemorrhage*	193	Moderate	Remote
		M	Carcinoma*	232	Moderate	Remote
1417	38	M	Agitation*	135	Moderate	None
1507	33	F	**Adjustment disorder/relational problems**[c,d]	818	Severe	None
1509	49	F	Chest pain*	118	Moderate	Remote
1721	50	F	Hematoma*	2	Moderate	None
			Bronchitis	484	Moderate	None
1905	50	M	**Chest tightness**[c,d]	765	Moderate	None
			Coronary Artery Disease[c,d]	787	Moderate	None
2102	22	M	**Attempted suicide**[c,d]	647	Severe	None
2113	52	M	Chest pain*	150	Moderate	None
2120	51	F	Palpitations*	20	Severe	Remote

13 6

Table 9. Summary of Open-Label Serious Adverse Experiences (C1538a/301/NA/US and C1538a/302/NA/US) (continued)

Patient Number	Age	Sex	Adverse Experience[a]	Onset (Study Day)	Severity	Relationship to Study Drug
Modafinil 300 mg/Study 301 (continued)						
2216	60	M	Coronary atherosclerosis[c,d]	806	Severe	None
			Quadruple bypass surgery[c,d]	813	Severe	None
Modafinil 300 mg/Study 302						
0106	45	F	Hysterectomy surgery*	105	Severe	None
0212	20	F	Pyelonephritis*	23	Severe	Possible
0306	54	M	Accidental injury*	-32	Severe	None
0405	26	M	Neoplasia*	-38	Moderate	None
			Rhinitis*	-38	Moderate	None
0504	42	M	Exertional dyspnea[c,d]	787	Moderate	None
			Third Degree Atrio-Ventricular Heart Block[c,d]	836	Severe	None
0908	47	M	Chest pain*	65	Severe	None
0909	26	M	Toxic encephalopathy[c,d]	762	Moderate	Remote
1002	60	M	Lower back muscle spasms[c,d]	635	Severe	None
1206	52	M	Chest pain	381	Moderate	None
			Chest pain	381	Moderate	None
			Angina pectoris	571	Severe	None
			Speech disorder	585	Severe	None
			Abnormal vision	585	Severe	None
1505	60	F	Infection*	171	Severe	None
			Myocardial infarction[c,d]	739	Mild	None
			Congestive heart failure[c,d]	791	Severe	None
1519	53	F	Lung disorder*	125	Severe	None
1704[e]	45	F	Accidental overdose*	220	Moderate	None
1904	37	M	Accidental injury	540	Life Threatening	Possible
2012	63	M	Lung disorder*	106	Severe	None
2019	64	M	Pneumonia*	176	Moderate	None
Modafinil 200 mg/ Study 301						
0410	26	F	Leukopenia*	-87	Mild	Possible
0505	52	F	Thyroid goiter	829	Moderate	Possible
			Leukopenia* (neutropenia)	-87	Mild	Possible
1210	31	F	Pruritus	564	Mild	Possibly

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ATTACHMENT 1

Table 9. Summary of Open-Label Serious Adverse Experiences (C1538a/301/NA/US and C1538a/302/NA/US) (continued)

Patient Number	Age	Sex	Adverse Experience[a]	Onset (Study Day)	Severity	Relationship to Study Drug
Modafinil 200 mg/Study 301 (continued)						
1423	67	F	**Accidental Injury***	39	Moderate	None
			Cardiovascular disorder	355	Life Threatening	None
			Cardiovascular disorder	392	Moderate	None
			Lung edema	392	Life Threatening	None
			Coronary artery disorder	393	Life Threatening	None
			Cardiovascular disorder	393	Life Threatening	None
1911	32	M	**Headache**	-1	Moderate	None
Modafinil 200 mg/Study 302						
0601	35	M	**Broken pelvis[c,d]**	425	Moderate	None
1506	53	M	Dyspepsia*	5	Moderate	Possible
1516	53	F	**Accidental Injury**	-6	Severe	None

a: COSTART coding symbol.
b: Accidental overdose by patient's 2-year-old daughter. Information gathered from MedWatch.
c: Occurred after database cutoff.
d: Adverse Experience Term from Case Report Form.
e: Accidental overdose by patient's 3-year old son.
Notes:
*Previously reported serious adverse experiences are marked with an asterisk; new adverse experiences are indicated by bolded text.
Patients 0211 from Study 301 and Patients 1906 and 1412 from Study 302 appear in error in Listing 3.0.1 as having serious adverse experiences. These patients are excluded from the above table.
NR = Not reported.
Source: Appendix 1.0, Listing 3.0.1.

No new pattern or trend is apparent in this list of serious adverse experiences.

3.3.5 Clinical Laboratory Tests (C1538a/301/NA/US and C1538a/302/NA/US)

All values for laboratory tests collected at Baseline, at each of the study visits, and at Endpoint (defined as the last visit for all patients), as well as supplemental assessments and clinical laboratory normal ranges, are presented in Appendices 1.1 to 3.0. Cutpoints for clinically significant laboratory values are found in Appendix 10.0.

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ATTACHMENT 2

3.2 Patient Population - Open-Label C1538a/301/NA/US and C1538a/302/NA/US

3.2.1 Patient Disposition (C1538a/301/NA/US and C1538a/302/NA/US)

A total of 478 patients entered the 40-week open-label study. Of these patients, 302 (63%) have completed the 40-week, 48-week, or are ongoing in further open-label extension. Overall, 13% of patients discontinued due to lack of study medication efficacy. Most of these were from the highest average dose group, as would be expected if patients moved to a higher dose in an attempt to reach therapeutic levels before discontinuing. Only 10% of patients discontinued due to adverse experiences. Most of these discontinuations were from the lowest dose group, which is also expected for patients sensitive to modafinil that would not want to risk increased severity or frequency of AEs by moving to a higher dose, or who might reduce their modafinil dose for safety reasons. The 40-week study has been completed, the 48-week study is ongoing, and further open-label extension phases are ongoing. Patient disposition is shown in the following table.

Table 1. Open-Label Disposition of Patients* (C1538a/301/NA/US and C1538a/302/NA/US)

	Average Daily Dose			
	Modafinil 400 mg[a] N (%)	Modafinil 300 mg[b] N (%)	Modafinil 200 mg[c] N (%)	Modafinil Combined N (%)
Patients started in open-label treatment	112	277	89	478
Discontinuations from open-label:				
Lack of study medication efficacy	42 (38%)	18 (7%)	4 (5%)	64 (13%)
Adverse experience	10 (9%)	18 (6%)	22 (25%)	50 (10%)
Patient noncompliance	6 (5%)	8 (3%)	6 (7%)	20 (4%)
Patient withdrew consent	10 (9%)	3 (1%)	8 (9%)	21 (4%)
Lost to follow-up	5 (5%)	2 (1%)	5 (6%)	12 (3%)
Protocol violation	1 (1%)	0	0	1 (<1%)
Other	2 (2%)	4 (1%)	2 (2%)	8 (2%)
Completed 40-week or 48-week open-label treatment phases, or continuing in open-label	36 (32%)	224 (81%)	42 (47%)	302 (63%)

*From database up to 6/2/97 cut-off date.
a: 400 mg: aversge daily dose ≥350 mg
b: 300 mg: aversge daily dose ≥250 mg and <350
c: 200 mg: aversge daily dose <250

3.2.2 Overall Exposure to Treatment (C1538a/301/NA/US and C1538a/302/NA/US)

A total of 478 patients were exposed to modafinil treatment for the first 8 weeks of open-label study; 209 patients had reached open-label extension week 48 by the data cut-off date. Overall treatment exposure by average daily dosage is presented in the table below.

Table 2. Open-Label Patient Exposure to Treatment (C1538a/301/NA/US and C1538a/302/NA/US)

Duration of Exposure	Average Daily Dose			
	Modafinil 400 mg n (%)	Modafinil 300 mg n (%)	Modafinil 200 mg n (%)	Modafinil Combined n (%)
OL Week 1-8	112 (100%)	277 (100%)	89 (100%)	478 (100%)
OL Week 9-16	103 (92%)	252 (91%)	64 (72%)	419 (88%)
OL Week 17-24	85 (76%)	243 (88%)	59 (66%)	387 (81%)
OL Week 25-32	68 (61%)	242 (87%)	57 (64%)	367 (77%)
OL Week 33-40	57 (51%)	241 (87%)	56 (63%)	354 (74%)
OLE Week 1-8	48 (43%)	238 (86%)	52 (58%)	338 (71%)
OLE Week 9-16	31 (28%)	239 (86%)	45 (51%)	315 (66%)
OLE Week 17-24	27 (24%)	234 (85%)	42 (47%)	303 (63%)
OLE Week 25-32	24 (21%)	226 (82%)	42 (47%)	292 (61%)
OLE Week 33-40	19 (17%)	210 (76%)	37 (42%)	266 (56%)
OLE Week 41-48	16 (14%)	160 (58%)	33 (37%)	209 (44%)

OL = Open-label (40 weeks)
OLE = Open-label extension (48 weeks)
Source: Table 2.0.0

In the 478 patients studied, there was a mean (SD) modafinil exposure of 416 (229) days, with an average dose of 305 mg/d. A summary of study medication exposure and actual average dose by mean dosage group is presented in the table below.

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Table 8. Summary of Open-Label Adverse Experiences Leading to Discontinuation (C1538a/301/NA/US and C1538a/302/NA/US)

Patient Number	Age	Sex	Adverse Experience[a]	Onset (Study Day)	Severity	Relationship to Study Drug	Drug Stop Day
Modafinil 400 mg/Study 301							
0502*	53	F	Atrial arrhythmia	116	Moderate	Possible	244
			ECG abnormality	129	Moderate	Possible	
1201	63	F	Anemia	296	Moderate	Remote	313
Modafinil 400 mg/Study 302							
0223	25	F	Unintended pregnancy	696	Mild	None	723
0304*	54	M	Emotional liability	55	Mild	Possible	108
			Depression	56	Mild	Possible	
0307*	52	F	Ventricular extrasystoles	1	Moderate	Remote	8
0402*	27	F	Unintended pregnancy	223	Mild	None	222
0708*	28	M	Infection	54	Moderate	None	90
1212*	64	M	Nervousness	11	Moderate	Possible	56
1306	50	F	Endometrial carcinoma[b]	284	Severe	Remote	255
1711*	51	M	Cerebrovascular accident[b]	118	Severe	Remote	118
1907*	55	M	Decreased Libido	-83	Moderate	Probable	78
			Arthralgia	28	Severe	Possible	
2308	32	F	Unintended pregnancy	742	Mild	None	742
Modafinil 300 mg/Study 301							
0104*	25	M	Cataplexy	117	Moderate	Possible	117
			Somnolence	117	Moderate	Possible	
0108	54	F	Mood change	898	Moderate	Probable	927
			Irritability	898	Moderate	Probable	
0307	51	F	Palpitations[b,c,d]	680	Severe	Possible	690
			Congestive Heart Failure[b,c,d]	689	Severe	Possible	690
			Cardiomegaly[b,c,d]	689	Severe	Possible	690
0606*	28	F	Neoplasia UG[b]	20	Severe	None	68
0701*	25	M	Intentional injury[b]	135	Life Threatening	None	135
0801*	47	F	Myalgia	81	Moderate	None	112
1016	23	F	Unintended pregnancy	687	Moderate	None	681
1102*	49	M	Nervousness	11	Severe	Probable	22
			Apathy	11	Severe	Probable	
1113*	36	F	Headache	-77	Mild	Probable	190
			Pain	-75	Mild	Probable	
			Dizziness	-63	Moderate	Probable	
			Metrorrhagia	-2	Moderate	Probable	
			Nervousness	1	Moderate	Probable	
			Infection	210	Moderate	None	
1121*	32	F	Metrorrhagia	-57	Moderate	Probable	109
1301*	52	F	Anxiety	35	Mild	Related	35
1506	60	F	Somnolence	532	Moderate	None	613
1915*	25	F	Asthma	19	Mild	Probable	55

ATTACHMENT 4

Table 8. Summary of Adverse Experiences Leading to Discontinuation (C1538a/301/NA/US and C1538a/302/NA/US) (continued)

Patient Number	Age	Sex	Adverse Experience[a]	Onset (Study Day)	Severity	Relationship to Study Drug	Drug Stop Day
Modafinil 300 mg/Study 301 (continued)							
2115*	22	F	Anxiety	87	Moderate	Probable	100
2214*	56	F	Tremor	18	Mild	Probable	20
			Cardiovascular disorder	18	Mild	Probable	
Modafinil 300 mg/Study 302							
0108*	35	F	Arthritis	10	Mild	Possible	23
0202	53	M	Increased cataplexy[c,d]	569	Moderate	Possibly	723
0212	20	F	Pregnancy[c,d]	745	Moderate	None	757
0215	50	F	Increased cataplexy[c,d]	490	Moderate	Remote	566
0303*	66	M	Sleep disorder	-95	Moderate	Probable	13
			Cataplexy	-95	Moderate	Related	
1005*	57	M	Diarrhea	-39	Moderate	Remote	55
			Nervousness	8	Mild	Remote	
			Nervousness	29	Moderate	Remote	
1904	37	M	Accidental Injury[b]	540	Life Threatening	Possible	532
2009*	26	F	Unintended pregnancy	18	Moderate	None	15
2201	20	F	Unintended pregnancy	564	Moderate	None	616
Modafinil 200 mg/Study 301							
0111*	47	F	Chest pain	2	Moderate	Possible	4
0116*	22	M	Dizziness	24	Mild	Remote	64
			Headache	24	Mild	Remote	
			Nausea	24	Mild	Remote	
0306*	63	F	SGPT increase	170	Moderate	Probable	179
			Liver function abnormality	170	Moderate	Probable	
			Alkaline phosphatase increase	170	Moderate	Probable	
0310*	33	F	Nervousness	50	Moderate	Related	50
0702*	43	F	Depression	149	Moderate	None	142
0705*	31	M	Nausea	39	Mild	Probable	69
1103*	20	F	Nervousness	6	Severe	Probable	11
1109*	53	F	Palpitations	2	Severe	Related	6
			Headache	2	Mild	Possible	
1115*	49	F	Alcohol intolerance	18	Moderate	None	18
1118*	23	F	Anxiety	1	Moderate	Related	17
1202	39	M	Liver function abnormality	290	Moderate	Possible	373
			Leukopenia (verbatim: neutropenia)	290	Moderate	Possible	

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ATTACHMENT 4

Table 8. Summary of Adverse Experiences Leading to Discontinuation (C1538a/301/NA/US and C1538a/302/NA/US) (continued)

Patient Number	Age	Sex	Adverse Experience[a]	Onset (Study Day)	Severity	Relationship to Study Drug	Drug Stop Day
Modafinil 200 mg/Study 301 (continued)							
1206*	20	F	Unintended pregnancy	83	Moderate	Remote	83
1210	31	F	Pruritus[b]	564	Mild	Possibly	587
1404*	54	F	Depression	29	Severe	Probable	35
1503	46	F	Goiter	626	Mild	Remote	626
1901*	44	M	Nervousness	8	Mild	Probable	8
			Anxiety	8	Mild	Probable	
Modafinil 200 mg/Study 302							
0213*	39	F	Nausea	1	Moderate	Related	6
0219*	22	F	Nervousness	-14	Mild	Probable	170
			Nervousness	-1	Moderate	Probable	
			Somnolence	-1	Moderate	Probable	
0502*	29	F	Unintended pregnancy	242	Severe	None	240
0707*	39	F	Asthenia	7	Severe	Probable	29
			Nervousness	7	Severe	Probable	
0805*	29	F	Nausea	17	Moderate	Related	38
			Vomiting	17	Mild	Related	
0818*	22	M	Hemoptysis	79	Mild	Remote	103
			Melena	99	Mild	Remote	
1506*	53	M	Dyspepsia[b]	5	Moderate	Possible	6

a: COSTART coding symbol.
b: This adverse experience also was coded as a Serious Adverse Experience
c: These discontinuations occurred after the database cut-off date.
d: Adverse Experience Term from Case Report Form.

Notes:

*Previously reported open-label patient discontinuations are marked with an asterisk; new patient discontinuations are indicated by bolded text.

Listing 3.0.4 includes all patients who discontinued study medication due to an adverse experience who may or may not have discontinued from the study due to adverse experiences. The above table and narratives found in Appendix 6.0 include only patients who discontinued from open-label studies 301 or 302.

Source: Appendix 1.0, Listing 3.0.4.

Though fewer than 11% of the total population discontinued from the open-label phase of the study, many of those that did (50%) were for Nervous System experiences. Complete narratives for each of the patients summarized in the table above who discontinued due to adverse experiences are found in Appendix 6.0.

3.3.3.1 New Adverse Experiences Resulting in Patient Discontinuation (C1538a/301/NA/US and C1538a/302/NA/US)

Adverse experiences that resulted in patient discontinuation from study that were not previously reported in the double-blind or open-label phases of C1538a/301/NA/US or C1538a/302/NA/US include the following:

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ATTACHMENT 5

Table 6. Summary of Common[a] Open-Label Emergent Adverse Experiences (C1538a/301/NA/US and C1538a/302/NA/US)

		Average Daily Dose			
	Statistic	Modafinil 400 mg (n = 112)	Modafinil 300 mg (n = 277)	Modafinil 200 mg (n = 89)	Modafinil Combined (n = 478)
Number of Patients with at Least One Open-Label Emergent Adverse Experience	n (%)	107 (96%)	259 (94%)	82 (92%)	448 (94%)
Body as a Whole					
Headache	n (%)	50 (45%)	128 (46%)	41 (46%)	219 (46%)
Infection	n (%)	20 (18%)	103 (37%)	24 (27%)	147 (31%)
Pain	n (%)	13 (12%)	54 (20%)	10 (11%)	77 (16%)
Flu Syndrome	n (%)	10 (9%)	42 (15%)	8 (9%)	60 (13%)
Accidental Injury	n (%)	7 (6%)	41 (15%)	8 (9%)	56 (12%)
Back Pain	n (%)	11 (10%)	29 (11%)	8 (9%)	48 (10%)
Allergic Reaction	n (%)	5 (5%)	24 (9%)	4 (5%)	33 (7%)
Chest Pain	n (%)	2 (2%)	15 (5%)	10 (11%)	27 (6%)
Abdominal Pain	n (%)	4 (4%)	15 (5%)	6 (7%)	25 (5%)
Fever	n (%)	2 (2%)	15 (5%)	3 (3%)	20 (4%)
Neck Pain	n (%)	6 (5%)	11 (4%)	3 (3%)	20 (4%)
Cardiovascular					
Hypertension	n (%)	2 (2%)	10 (4%)	6 (7%)	18 (4%)
Palpitations	n (%)	1 (1%)	6 (2%)	6 (7%)	13 (3%)
Digestive					
Dyspepsia	n (%)	12 (11%)	44 (16%)	11 (12%)	67 (14%)
Tooth Disorder	n (%)	14 (13%)	39 (14%)	10 (11%)	63 (13%)
Nausea	n (%)	7 (6%)	36 (13%)	14 (16%)	57 (12%)
Diarrhea	n (%)	6 (5%)	24 (9%)	6 (7%)	36 (8%)
Dry Mouth	n (%)	2 (2%)	21 (8%)	8 (9%)	31 (7%)
Anorexia	n (%)	2 (2%)	4 (1%)	6 (7%)	12 (3%)
Constipation	n (%)	3 (3%)	4 (1%)	5 (6%)	12 (3%)
Metabolic / Nutrition					
Peripheral Edema	n (%)	6 (5%)	4 (1%)	1 (1%)	11 (2%)
Musculoskeletal					
Myalgia	n (%)	8 (7%)	21 (8%)	5 (6%)	34 (7%)
Arthritis	n (%)	4 (4%)	16 (6%)	0	20 (4%)
Arthralgia	n (%)	3 (3%)	11 (4%)	5 (6%)	19 (4%)
Nervous					
Nervousness	n (%)	8 (7%)	28 (10%)	16 (18%)	52 (11%)
Depression	n (%)	10 (9%)	28 (10%)	10 (11%)	48 (10%)
Cataplexy	n (%)	8 (7%)	30 (11%)	7 (8%)	45 (9%)
Anxiety	n (%)	2 (2%)	17 (6%)	15 (17%)	34 (7%)
Somnolence	n (%)	10 (9%)	17 (6%)	5 (6%)	32 (7%)
Dizziness	n (%)	6 (5%)	17 (6%)	6 (7%)	29 (6%)
Insomnia	n (%)	2 (2%)	15 (5%)	9 (10%)	26 (5%)
Respiratory					
Rhinitis	n (%)	15 (13%)	50 (18%)	9 (10%)	74 (16%)
Sinusitis	n (%)	6 (5%)	36 (13%)	10 (11%)	52 (11%)
Cough	n (%)	7 (6%)	32 (12%)	6 (7%)	45 (9%)
Pharyngitis	n (%)	9 (8%)	20 (8%)	9 (10%)	39 (8%)
Bronchitis	n (%)	4 (4%)	25 (9%)	7 (8%)	36 (8%)
Urogenital					
Urinary Tract Infection	n (%)	4 (4%)	14 (5%)	4 (5%)	22 (5%)
Dysmenorrhea	n (%)	3 (3%)	9 (3%)	5 (6%)	17 (4%)

a: ≥5% of the safety evaluable population in any dosage group.
Source: Table 3.1.0; Appendix 1.0, Listing 3.0.0.

ATTACHMENT 6

Table 7. Summary of Common[a] Drug-Related[b] Open-Label Emergent Adverse Experiences (C1538a/301/NA/US and C1538a/302/NA/US)

		Average Daily Dose			
	Statistic	Modafinil 400 mg (n = 112)	Modafinil 300 mg (n = 277)	Modafinil 200 mg (n = 89)	Modafinil Combined (n = 478)
Number of Patients with at Least One Open-Label Emergent Related Adverse Experience	n (%)	9 (8%)	53 (19%)	40 (45%)	102 (21%)
Body as a Whole					
Headache	n (%)	0	8 (3%)	5 (6%)	13 (3%)
Infection	n (%)	0	0	0	0
Pain	n (%)	0	0	0	0
Flu Syndrome	n (%)	0	0	0	0
Accidental Injury	n (%)	0	0	0	0
Back Pain	n (%)	0	0	0	0
Allergic Reaction	n (%)	0	0	0	0
Chest Pain	n (%)	0	0	0	0
Abdominal Pain	n (%)	0	0	0	0
Fever	n (%)	0	0	0	0
Neck Pain	n (%)	0	0	1 (1%)	1 (<1%)
Cardiovascular					
Hypertension	n (%)	0	1 (<1%)	0	1 (<1%)
Palpitations	n (%)	0	2 (<1%)	4 (4%)	6 (1%)
Digestive					
Dyspepsia	n (%)	0	1 (<1%)	1 (1%)	2 (<1%)
Tooth Disorder	n (%)	0	0	0	0
Nausea	n (%)	1 (<1%)	5 (2%)	3 (3%)	9 (2%)
Diarrhea	n (%)	0	2 (<1%)	0	2 (<1%)
Dry Mouth	n (%)	1 (<1%)	7 (3%)	3 (3%)	11 (2%)
Anorexia	n (%)	1 (<1%)	2 (<1%)	2 (2%)	5 (1%)
Constipation	n (%)	0	0	1 (1%)	1 (<1%)
Metabolic / Nutrition					
Peripheral Edema	n (%)	0	1 (<1%)	0	1 (<1%)
Musculoskeletal					
Myalgia	n (%)	0	0	0	0
Arthritis	n (%)	0	0	0	0
Arthralgia	n (%)	0	0	0	0
Nervous					
Nervousness	n (%)	3 (3%)	13 (5%)	13 (15%)	29 (6%)
Depression	n (%)	0	1 (<1%)	1 (1%)	2 (<1%)
Cataplexy	n (%)	1 (<1%)	1 (<1%)	2 (2%)	4 (1%)
Anxiety	n (%)	1 (<1%)	7 (3%)	10 (11%)	18 (4%)
Somnolence	n (%)	2 (2%)	6 (2%)	3 (3%)	11 (2%)
Dizziness	n (%)	0	1 (<1%)	1 (1%)	2 (<1%)
Insomnia	n (%)	1 (<1%)	2 (<1%)	5 (6%)	8 (2%)
Respiratory					
Rhinitis	n (%)	0	0	0	0
Sinusitis	n (%)	0	0	0	0
Cough	n (%)	0	0	0	0
Pharyngitis	n (%)	0	1 (<1%)	0	0
Bronchitis	n (%)	0	0	0	0
Urogenital					
Urinary Tract Infection	n (%)	0	0	0	0
Dysmenorrhea	n (%)	0	0	0	0

a: ≥5% of the safety evaluable population for all adverse experiences in any dosage group.
b: Includes probably related and related events.
Source: Table 3.1.2; Appendix 1.0, Listing 3.0.0.

ATTACHMENT 7

Table 11. Summary of Open-Label GGT Mean Observed and Change From Baseline Values By Visit (C1538a/301/NA/US and C1538a/302/NA/US)

		Average Daily Dose			
Parameter	Statistic	Modafinil 400 mg	Modafinil 300 mg	Modafinil 200 mg	Modafinil Combined
GGT (IU/L)					
Observed Values at Open-label Baseline					
	n	110	271	86	467
	Mean ± S.D.	33.2 ± 37.5	32.0 ± 26.9	27.1 ± 25.2	31.3 ± 29.4
Change from Open-label Baseline Values					
Week 2	n	107	265	79	451
	Mean ± S.D.	0.1 ± 15.3	-0.02 ± 9.1	-0.3 ± 10.3	-0.03 ± 11.0
Week 8	n	104	248	67	419
	Mean ± S.D.	7.7 ± 22.4	6.7 ± 21.9	3.0 ± 10.3	6.3 ±20.7
Week 24	n	77	234	51	362
	Mean ± S.D.	10.4 ± 28.1	8.0 ± 25.6	3.4 ± 11.0	7.8 ± 24.7
Week 40	n	53	235	53	341
	Mean ± S.D.	10.9 ± 23.1	5.6 ± 21.4	6.3 ± 20.5	6.6 ± 21.6
Week 88	n	12	124	21	157
	Mean ± S.D.	16.4 ± 37.6	11.2 ± 18.3	3.5 ± 11.2	10.6 ± 19.8
OL Endpoint	n	110	269	82	461
	Mean ± S.D.	8.6 ± 28.1	5.5 ± 19.0	3.0 ± 20.2	5.8 ± 21.8

Source: Tables 4.0.0 and 4.0.1; Appendix 1.1

Shifts (C1538a/301/NA/US and C1538a/302/NA/US)

There were no clinically meaningful trends in the number of patients with shifts to values above the upper limit of normal (ULN) for total bilirubin, or shifts to below the lower limit of normal (LLN) for total protein and albumin.

Patients with shifts from baseline to above the ULN in alkaline phosphatase ranged from less than 1% at Week 2 to 7% at Week 88. A summary of patients with shifts to above the ULN in alkaline phosphatase is presented in the table below. Alkaline phosphatase values for individual patients are listed in Appendix 1.1.

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Table 22. Modafinil UK and Ireland Named Patient Use - Patients Who Discontinued Due to Adverse Experiences or Had a Serious Adverse Experience

Subject	Sex	Age at Start	Modafinil Dose	Adverse experience (AE)	Discontinued Due to AE	Serious	Date of Last Dose	Duration of Treatment	Relationship to Study Drug
[redacted]181233	M	63	not available	Vertigo	Yes	No	04/18/97	3 days	Probable
[redacted]091030	F	66	200 mg	Pressure in head, difficulty breathing, irritable, cataplexy worsened, lack of energy	Yes	No	05/10/97	9 days	Probable
[redacted]170944	M	52	300 mg	Nausea, agitation, emotional changes	Yes	No	06/26/97	41 days	Probable
[redacted]220834	F	62	400 mg	Ankle and facial edema	Yes	No	08/07/97	109 days	Possible
[redacted]230245	M	52	400mg	Myalgia	Yes	No	09/16/97	83 days	Probable
[redacted]240630	F	67	200mg	Depression, worsening cataplexy, tiredness	Yes	No	11/24/97	33 days	Probable
[redacted]011166	F	31	400mg	Nightmares, poor concentration, low mood	Yes	No	12/12/97	41 days	Probable
[redacted]A110359	M	38	400mg	Itchy skin rash arms and legs	Yes	No	12/12/97	15 days	Possible
[redacted]051139	F	57	200mg	Worsening cataplexy	Yes	Yes	20/02/97	1 day[a]	Possible
[redacted]010832	F	64	400mg	Increased cataplexy leading to falls	Yes	Yes	02/05/97	36 days[a]	Probable

a: For SAE s, treatment duration is at time of SAE occurrence.

ATTACHMENT 9

6.2 Studies Conducted in Canada

Five studies and one compassionate use program were ongoing or were initiated in Canada since the cut-off date for data inclusion in the modafinil NDA 20-717. Available information regarding deaths, serious adverse experiences and discontinuations due to adverse experiences are summarized below.

6.2.1 Study 94003

Draxis Study 94003 was a double-blind, placebo-controlled crossover study in patients with narcolepsy, conducted from January 25, 1995 to January 19, 1996. A long-term, open-label portion of the study was conducted from March 11, 1995 to May 25, 1996.

No deaths or serious adverse experiences were reported during the conduct of this study. Three patients discontinued due to adverse experiences during Part 1 (short-term), one of whom was taking placebo at the time. One patient discontinued due to adverse experiences during Part 2 (long-term). These discontinuations are summarized in the following table.

Table 23. Discontinuations Due to Adverse Experiences in Draxis Study 94003

Patient Identifier	Age	Sex	Modafinil Dosage	Adverse Experience[a]	Onset (Study Day)	Severity	Relationship to Study Drug	Drug Stop Day
01-01	49	M	400 mg	Nausea	2	Moderate	Probably	NR
				Headache		Moderate	Probably	
				Anxiety		Moderate	Probably	
				Repetitive movements		Severe	Probably	
05-05	30	M	200 mg	Rash	29	Moderate	Unknown	34
05-11	20	M	Placebo	Chest pain	7	Severe	Probably	11
02-13	41	F	Maximum 500 mg	Headaches	50	Severe	Probably	57
				Melancholia	39	Moderate	Unknown	
				Lethargy	39	Moderate	Unknown	

NR = Not reported

Narratives and case report forms for these patients are found in Appendices 11.1 and 11.2.

6.2.2 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 or pregnancy, as summarized in the following table.

ATTACHMENT 10

Table 24. Discontinuations Due to Adverse Experiences in Draxis Compassionate Use Program

Subject	Sex	Birth Year	Modafinil Dose	Adverse Experience
[redacted]	F	1955	200 mg bid	pregnancy
	M	1941	100-200 mg bid	dyspepsia
	F	1974	200 mg bid	visual disturbance
	F	1947	200 mg, 100 mg bid	depression (seasonal)
	F	1940	200 mg bid	dyspepsia increased liver function test values
	F	1942	unknown	palpitations possible depression
	F	1956	300 mg qAM	epistaxis
	M	1949	100 mg "die"	palpitations dysphoria insomnia
	M	1925	200 mg bid	disrupted sleep increased leg movements

Case report forms were not consistently utilized in the Draxis compassionate use program. Therefore, case report forms and patient narratives for this study are not provided.

6.2.3 Military Studies in Canada

There were no deaths or serious adverse experiences reported in the four Canadian military studies: L40, L58, L136, and L188. One subject discontinued due to an adverse experience ("flu-like symptoms") from Study L58, but had not been treated with modafinil.

6.3 Studies Conducted by Lafon

Information regarding discontinuations due to AEs and SAEs from Lafon is provided through January 31, 1998.

6.3.1 Discontinuations due to Adverse Experiences Since NDA Filing ([redacted] Studies)

Twenty-two (22) patients discontinued due to adverse experiences in a series of six studies conducted by [redacted] These patients are summarized in the table below; case report forms (French and English translations) and narratives for these patients are found in Appendices 11.3 and 11.4.

ATTACHMENT 11

Table 25. Summary of Adverse Experiences Leading to Discontinuation: [redacted] Sponsored Studies

Patient Identifier	Age	Sex	Modafinil Dosage	Adverse Experience	Onset (Study Day)	Severity	Relationship to Study Drug	Drug Stop Day
[redacted] Study E1027								
	65	M	200 mg QD	Dyspnea[a, b]	20	Mild	None	73
	33	F	200 mg QD	Suicide[a,c]	549	Unknown	None	549
Study E1028								
31[redacted]	19	M	NR	Acute delirious outburst	NR	NR	NR	NR
45[redacted]	46	F	NR	Increased falls	NR	NR	NR	NR
				Increased hypnagogic hallucinations				
77[redacted]	61	M	NR	Increased facial twitches	NR	NR	NR	NR
84[redacted]	56	F	NR	Hospitalization for asthma[a]	NR	NR	NR	NR
[redacted] Study E1029								
[redacted]03	49	F	Placebo	Abdominal pain/ gastralgia	1	Medium	Probable	6
				Nausea	1	Mild	Probable	
[redacted]04	47	F	200 mg BID	Nausea	2	Intense	Probable	3
				Vomiting	2	Intense	Probable	
				Asthenia	2	Intense	Possible	
				Anorexia	2	Intense	Possible	
				Hot Flashes	2	Medium	Possible	
[redacted]021	40	F	200 mg BID	Palpitations	5	Mild	None	15
				Tremors	5	Medium	None	
			200 mg QD[d]	Depression[a]	15	NR	None	
				Anxiety	15	NR	None	
[redacted]026	61	F	200 mg BID	Nausea	1	Medium	Probable	3
				Ocular pain	1	Medium	Probable	
				Insomnia	1	Medium	Probable	
[redacted]046	64	F	Placebo	Diarrhea	5	Medium	Probable	9
[redacted]049	61	F	200 mg BID	Anxiety	4	Intense	Probable	10
				Insomnia	4	Intense	Probable	
[redacted]050	46	F	200 mg BID	Anxiety	8	Medium	Probable	13
				Myalgia	9	Mild	Probable	
				Thoracic tightness	9	Medium	Probable	
				Aggressiveness	9	Medium	Probable	
[redacted] Study E1043/Double-Blind Phase								
[redacted]01	75	F	NR	Increased stiffness	20	Average	NR	50
				Anxiety	30	Unobtrusive	NR	
				Sleep problems	30	Unobtrusive	NR	
[redacted]07	70	F	NR	Nausea	5	Average	Possible	13
				Flatulence	5	Average	Possible	
				Abdominal pain	5	Average	Possible	
				Headache	5	Average	Possible	
[redacted]05	78	F	NR	Increased fatigue	2	Average	NR	17
				Increased blood pressure	13	NR	NR	
				Palpitations	13	NR	NR	

ATTACHMENT 11

Table 25. Summary of Adverse Experiences Leading to Discontinuation: [redacted] Sponsored Studies (continued)

Patient Identifier	Age	Sex	Modafinil Dosage	Adverse Experience[a]	Onset (Study Day)	Severity	Relationship to Study Drug	Drug Stop Day
[redacted] Study E1043/Double-Blind Phase (cont)								
[redacted]07	75	M	NR	Insomnia	1	Unobtrusive	Possible	19
				Tingling in lower extremities	4	Average	Possible	
[redacted]08	77	F	NR	Hypertonia	4	Average	Possible	8
				Respiratory obstruction	4	Average	Possible	
				Tachycardia	4	Average	Possible	
				Instability on walking				
				Flatulence	4	Average	Possible	
[redacted] Study E1043/Open-Label Phase								
[redacted]/G02[a]	60	M	400 mg QD	Angina pectoris	4	NR	None	35
[redacted] Study E1044								
[redacted]11	9	M	NR	Insomnia	17	Discrete	Probable	34
[redacted] Study E1047								
[redacted]8	NR	NR	NR	Worsening problem with attention and concentration	NR	Intense	Likely	NR
[redacted]13	NR	NR	NR	Headache	1	Unobtrusive	NR	21
				Asthenia	1	Average	Likely	

a: This adverse experience also was coded as a Serious Adverse Experience
b: This adverse experience was also separately reported to the *Agence du Médicament* as a spontaneous event outside of a clinical trial.
c: This adverse experience resulted in death.
d: Patient took 200 mg BID until onset of SAE symptoms. Dose was then reduced to 200 mg QD.
e: Adverse experience information for this patient available as telephone contacts and is not included in double-blind CRF appearing in Appendix 11.4.
NR=Not reported.
Source: MedWatch Reports and Case Report Forms

6.3.2 Serious Adverse Experiences Since NDA Filing ([redacted] Studies)

Nine patients had serious adverse experiences in a series of four studies conducted by [redacted] and one study conducted by [redacted]. These experiences are summarized in the table below.

APPEARS THIS WAY ON ORIGINAL

ATTACHMENT 12

Table 26. Summary of Serious Adverse Experiences: [redacted] Sponsored Studies

Patient Identifier	Age	Sex	Modafinil Dosage	Adverse Experience	Onset (Treatment Day)	Severity	Relationship to Study Drug
Lafon Study E1027							
[redacted]	33	F	200 mg QD	Suicide	549	Unknown	None
	47	M	400 mg QD	Fall	~1108	Mild	None
				Infection	1213	Mild	None
				Dizziness/loss of consciousness	1230	Mild	None
	46	F	500 mg QD	Asthenia	512	Moderate	None
	65	M	200 mg QD	Dyspnea	20	NR	None
	60	F	300 mg QD	Malaise	25	Severe	Possible
				Vertigo	25	Severe	Possible
				Unconsciousness	25	Severe	Possible
				Disorientation	25	Severe	Possible
[redacted] Study E1028							
84[redacted]	56	F	NR	Hospitalization for asthma	NR	NR	NR
[redacted] Study E1029							
[redacted]021[b]	40	F	200 mg BID	Palpitations	5	Mild	None
				Tremors	5	Medium	
			200 mg QD[c]	Depression	15	NR	
				Anxiety	15	NR	
[redacted] Study E1043							
[redacted]G02	60	M	400 mg QD	Angina Pectoris	4	NR	None
[redacted] Study MOD02							
31-14	52	M	300 mg QD	Supraventricular tachycardia	1	Mild	Possible

a: This adverse experience was also separately reported to the *Agence du Médicament* as a spontaneous event outside of a clinical trial.
b[redacted] identifies these patients as discontinuations due to adverse experiences. Based on Cephalon review, hospitalization of these patients suggests SAE.
c: Patient took 200 mg BID until onset of SAE symptoms. Dose was then reduced to 200 mg QD.
NR=Not reported.
Source: MedWatch Reports and Case Report Forms

6.3.3 Serious Adverse Experiences and Discontinuations Due to Adverse Experiences Not Previously Reported in NDA 20-717 [redacted] Studies)

The five subjects appearing in the table below are identified by Lafon as having potentially serious adverse experiences for whom documentation in NDA 20-717 was limited to ISS Summary Table as event counts and individual [redacted] Study Reports. In the ISS, these subjects were not identified as having a serious adverse experience. Because these potentially serious adverse experiences were not described within NDA 20-717, additional clinical information is now listed.

[redacted]APPEARS THIS WAY ON ORIGINAL

ATTACHMENT 13

Table 27. Summary of Serious Adverse Experiences With Limited Presentation in NDA 20-717: [redacted]-Sponsored Studies

Patient Identifier	Age	Sex	Modafinil Dosage	Adverse Experience	Onset (Treatment Day)	Severity	Relationship to Study Drug
[redacted] Study Open 4-4 Inpatient							
1	30	M	800 QD max	Aggression, motor instability,	8	Moderate	NR
				Mannerisms, logorrhea, auditory hallucinations	15	Severe	NR
[redacted] Study 908 Inpatient							
E02 (1)	26	M	300 mg QD	Myoclonic movements	47	Moderate	Doubtful
[redacted] Study 823							
U19	31	F	100 mg bid	Psychomotor disorders,	2	Moderate	Definite
				Sleeping problems	7	Moderate	Possible
[redacted]20	24	F	100 mg bid	Delirium, automatisms, excitation	4	Moderate	Possible
Lafon Study - Open Pharmacokinetics							
101	86	F	300 mg QD	Equilibrium disorder,	1	NR	NR
				LOC,	1	NR	NR
				Hypertension (203/75 mmHG),	1	NR	NR
				Restlessness,	1	NR	NR
				Insomnia,	4	NR	NR
				Choreiform movements	2	NR	NR

NR=Not reported.
Source: Case report forms

The 12 subjects in the table below are identified as having potentially serious adverse experiences for whom no safety data was included in NDA 20-717 because no CRFs were available. [redacted] tabular information summaries and adverse experience information were available and have been reviewed for this submission. Subject #103 from Study 691/1-2 was the only subject in this group known to have discontinued from study due to an adverse experience. A narrative based on tabular information for this subject appears in Appendix 11.3, although the case report form is not provided.

Prior reporting of these adverse events has appeared in either the IND submission (#42,873 Serial #000 6/30/93) or the current (April 10, 1995) Investigator's Drug Brochure (Serial #044 4/26/95).

[redacted]APPEARS THIS WAY ON ORIGINAL

ATTACHMENT 14

Table 28. Summary of Serious Adverse Experiences Not Previously Reported in NDA 20-717: [redacted] Sponsored Studies

Patient Identifier	Age	Sex	Modafinil Dosage	Adverse Experience	Onset (Treatment Day)	Severity	Relationship to Study Drug
[redacted] Study 724/5-10							
301	62	M	400 mg QD max	Generalized epileptic attack	26	Severe	NR
303	79	M	400 mg QD max	Malaise, Epileptic attack	17 27	Severe NR	NR NR
[redacted] Study 702/8-3							
101	NR ("healthy young")		600 mg (1 dose)	Oneiric visual impressions, nervous irritation, Insomnia	1	Severe	NR
102	NR ("healthy young")		600 mg (1 dose)	Oneiric visual impressions, Insomnia	1	Severe	NR
[redacted] Study Open/1-5							
[redacted]OI	24	M	200 mg (1 dose)	Excitation, mydriasis, headache, visual hallucinations	1	Severe	NR
[redacted]	30	M	200 mg (1 dose) 400 mg (1 dose)	Insomnia, mydriasis, clonic movements, visual disturbance, tremor	1	Severe	NR
[redacted] Study 698/6-2							
604[redacted]	89	M	600 mg (1 dose)	Agitation, movement disorder, insomnia	1	Severe	Possible
[redacted] Study 797/6-3							
[redacted]04	70	F	100 mg bid	Dyskinesia, delirious/agitated, sleep problems	2	Severe	NR
[redacted] Study 707/1-11							
105	22	M	600 mg (1 dose)	Hypertension (systolic BP=240 mmHg), tachycardia	1	Severe	NR
[redacted] Study 691/1-2							
103*	70	M	200 mg bid	Attention deficit/ hyperactivity, aggressive delirium	2	NR	NR
[redacted] Study 798/5-9							
F4	82	F	100 mg bid	Extrapyramidal syndrome, tremor, hypertension	2	Mild	Definite
H1	86	F	100 mg bid	Tics	2	Mild	NR

*This patient was discontinued from study. The CRF for this patient was lost in flood salvage operations and is not included. A narrative based on existing tabular summaries from [redacted] is found in Appendix 11.3.
NR=Not reported.
Source: [redacted] tabular information summaries

ATTACHMENT 15

Table 29. Summary of Serious Adverse Experiences: Foreign Spontaneous Reports Outside Clinical Trial

Patient Identifier	Age	Sex	Modafinil Dosage	Adverse Experience	Onset (Treatment Day)	Severity	Relationship to Study Drug[a]
[redacted]	18	M	Up to 700 mg QD[b]	Delirium with agitation and cries	89	Severe	Causality not attributed
	56	M	300 mg QD	Malaise with vision abnormalities	—[c]	Moderate	Doubtful
	85	M	200 mg QD	Hemipligia	—[d]	Severe	Doubtful
	NR	M	200-300 mg QD	Gastritis hemorrhagic	NR	NR	Doubtful
	32	NR	200 mg QD	Anaphylactic shock, Angiodema (Quinkcke's edema), Urticaria	1	Life-threatening	NR

a: Relationship per Lafon.
b: Patient was prescribed modafinil 400 mg QD, but took up to 700 mg QD with the goal of improving physical performance.
c: Exact therapy dates unknown. Patient had received modafinil for approximately 1 year at the time of the event.
d: Exact therapy dates unknown. Patient had received modafinil for approximately 3 years at the time of the event.
e: No patient initials provided. Cephalon SAE Report Number CEPH-1538-98-0015b
NR=Not reported.
Source: MedWatch and Lafon Pharmacovigilance Reports

An additional two patients had serious adverse experiences reported as a spontaneous event outside of a clinical trial to the *Agence du Médicament*. However, these patients were actually involved in Lafon clinical trials, resulting in duplicate reporting of their SAEs. Therefore, the SAEs for these latter patients are summarized in the Lafon clinical trial Sections 6.3.1 and 6.3.2.

7. LITERATURE REVIEW

Published information about potential uses of modafinil or clinical studies of modafinil was identified via a survey of the world literature. Computer searches by trained information retrieval specialists [redacted] included searches of the Medline, BIOSIS, Embase, Pharmaceutical News Index, and other databases (see Appendix 12.0). Key words utilized in the searches were "Cephalon", "modafinil", and "narcolepsy". Pharmaceutical industry and scientific general interest publications also were monitored for information relative to modafinil. The searches were conducted without restriction to language. The searches, current as of December 22, 1997, resulted in the identification of more than 200 articles, letters, reviews, and press releases.