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

DATE: **March 3, 2006**

TO: Thomas Laughren, M.D., Director
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and
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and
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THROUGH: Mark Avigan, M.D., C.M., Director
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Office of Drug Safety (ODS)

FROM: Andrew Mosholder, M.D., M.P.H., Epidemiologist

SUBJECT: Psychiatric Adverse Events in Clinical Trials of Drugs for Attention Deficit Hyperactivity Disorder (ADHD)

PID: D060163

DRUGS:

Table 1. Drugs indicated for ADHD included in this review

Approved Products			
NDA #	**Name**	**Company**	**Date of Approval**
21-303	Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules	Shire Pharmaceuticals, Inc.	10/11/2001
21-278	Focalin (dexmethylphenidate HCL) Tablets	Novartis Pharmaceuticals Corporation	11/13/2001
21-802	Focalin XR (dexmethylphenidate HCL) Extended-Release Capsules	Novartis Pharmaceuticals Corporation	5/26/05
21-121	Concerta (methylphenidate HCL) Extended-Release Tablets	McNeil Consumer and Specialty Pharmaceuticals	8/11/2000
21-259	Metadate CD (methylphenidate HCL) Extended-Release Capsules	UCB Pharma, Inc.	4/3/2001
21-284	Ritalin LA (methylphenidate HCL) Extended-Release Capsules	Novartis Pharmaceuticals Corporation	6/5/2002
21-411	Strattera (atomoxetine HCL) Capsules	Eli Lilly & Company	11/26/2002
Pending NDAs/sNDAs			
20-717 S-019	Provigil (modafinil) Tablets	Cephalon, Inc.	pending
21-514	Methylphenidate transdermal system (MTS)	Noven Pharmaceuticals, Inc (Shire is a co-development partner with Noven	pending

Additionally, in study SPD485201 there was an open-label run-in period prior to randomization that enrolled 93 patients (80 eventually were randomized), and during this run-in period there were 2 aggression events.

There were also clinical data from 9 bioavailability studies (4 involving pediatric ADHD patients), and 2 special skin sensitization studies in healthy adults. Review of the sponsor's listing of adverse events showed that in the biopharmaceutics trials, one child receiving Concerta, and 1 adult administered MTS buccaly experienced psychosis/mania events. In the two open-label special skin sensitization protocols, which together exposed 315 healthy adult volunteers, there were 6 psychosis/mania events and one aggression event. Data from a special study of abuse potential in adults (N17-007) showed 2 psychosis/mania events with MTS, and four such events with the active controls.

The sponsor identified no relevant adverse events occurring after treatment discontinuation. Also, there were no serious psychiatric adverse events in the miscellaneous category.

D. Modafinil (NDA 20-717 S-019, Cephalon, Inc.)

Modafinil (Provigil, marketed by Cephalon, Inc.) is a non-sympathomimetic stimulant marketed for the treatment of excessive daytime sleepiness associated with sleep disorders. An indication for ADHD is under review, and will be the topic at the March 23 Psychopharmacologic Drugs Advisory Committee meeting.

With respect to psychotic adverse reactions, the current modafinil labeling notes (in the Precautions section) one such episode in a normal volunteer:

> One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of PROVIGIL and sleep deprivation. There was no evidence of psychosis 36 hours after drug discontinuation.[3]

Analysis of Psychiatric Adverse Events in Response to Approvable Letter

The sponsor provided the following analysis in reply to our September 14, 2005 request as part of their response to the approvable letter for the indication of ADHD.

[3] Provigil prescribing information available at www.provigil.com

Table D1. Frequency of patients with psychiatric adverse events in ADHD trials (response to approvable letter)

Study design	Treatment	N	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	308	0	0	5
DB	Modafinil	664	2	4	9
Open	Modafinil	799	2	0	14

Analysis in response to FDA request 9-14-05

The sponsor also provided data on the adverse events of interest in a separate submission 1-6-06, responding specifically to the agency's request letter of 9-14-05. It appeared that this later submission included additional clinical trial data, although a list of the specific studies included was provided only for the 1-6-06 submission, so this could not be verified.

Table D2. Frequency of patients with psychiatric adverse events in ADHD trials (sponsor's 1-6-06 submission)

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	366	39.87	0	0	5
DB	Modafinil	772	85.50	2	4	9
Open	Modafinil	924	383.53	2	0	14

There were no serious adverse events in the miscellaneous category.

There were more events in all categories among modafinil treated patients compared to placebo, but the exposure to modafinil was greater. It will be noted, however, that the frequency of these events during double blind treatment was higher than during open label treatment.

The table below displays the data for the subgroup of pediatric patients only (i.e., eliminating study 205 in adults, in which there were no events of interest).

Table D3. Frequency of pediatric patients with psychiatric adverse events in ADHD trials (from 1-6-06 submission)

Study design	Treatment	N	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events
DB	Placebo	308	32.55	0	0	5
DB	Modafinil	664	75.11	2	4	9
Open	Modafinil	799	369.35	2	0	14

It should be noted that the NDA review by the Division of Psychiatry Products identified two additional probable cases of aggression during double blind treatment, in study 207 (patients 410 and 411).[4]

[4] Drs. June Cai and Glenn Mannheim, Division of Psychiatry Products

In addition, the sponsor noted that there were no events in the miscellaneous category that met criteria for "serious."

With respect to events occurring after study treatment, one modafinil-treated subject (#410 in study 207) experienced formication (coded as psychosis) within 48 hours of treatment discontinuation, and one 6-year old female (subject 312-014016) was hospitalized for self-harmful behavior (putting a rope around her neck) two days after discontinuing open label treatment with modafinil. There were no psychiatric adverse events during the period from 48 hours to 30 days after treatment discontinuation.

One of the two psychosis/mania events during open label treatment required psychiatric hospitalization for a psychotic episode with suicidal ideation (patient 213-11002, an 8-year old boy who had a history of such symptoms, although this was apparently not known at study entry). This case was counted by the sponsor only in the psychosis/mania category, although it perhaps could have been counted as a suicidal event as well. The only two patients with serious psychiatric adverse events in these clinical trials were 312-014016 and 213-11002. (An additional case of suicidal ideation in a modafinil treated patient, requiring hospitalization, was included in the sponsor's safety update for the ADHD supplement (patient 016001 from ongoing Study 312), but this apparently occurred after the cutoff date for the present data set.[5])

Appendix table D displays the characteristics of the ADHD clinical trials. In addition, the sponsor provided data on the psychiatric events of interest from other indications. These data are summarized below.

Table D4. Frequency of patients with selected psychiatric adverse events in studies of other indications

Study design	Indication	Treatment	Patient years of exposure	Psychosis/mania events	Suicidal events	Aggression events	Miscellaneous serious events
DB	Excessive sleepiness	Placebo	96.65	1	0	0	1
DB	Excessive sleepiness	Modafinil	168.44	3	1	4	2
Open	Excessive sleepiness	Modafinil	1988.31	4	6	17	4
DB	Other*	Placebo	26.56	0	0	0	0
DB	Other*	Modafinil	98.37	8	2	13	6
Open	Other*	Modafinil	89.98	10	3	12	3

*Clinical pharmacology, depression, dementia, head trauma, and other disorders

[5] Dr. June Cai, FDA Division of Psychiatric Products, personal communication

N17-021	Multi	6-12	32 mos.	6.25-50 cm^2	191	-	-	Subjects from N17-018	Continued open label treatment	2004
SPD485-303	Multi	6-12	1 yr	12.5-37.5 cm^2	288 (ongoing)	-	-	Subjects from SPD485-102 and SPD485-302	Ongoing open label study	2006 projected. Interim data from June 2005

Abbreviations: mph methylphenidate; Xover crossover

Appendix Table D. ADHD safety and efficacy studies with modafinil included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration	Dose (mg/day)	N		Population	Comments	Study completion date
					Drug	Placebo			
205	6 (phase A) 7 (phase B)	Adults 18-57	6 wks	100, 200, 400 (fixed)	109 (74 phase A, 35 phase B)	75 (38 Phase A, 37 Phase B)	ADHD without psychiatric comorbidity	Included 8 week open label extension	2001
207	3	6-13	1 wk 4 way Xover	0, 100, 200, 300/400	46	44	ADHD	Included 8 wk open label extension	2000
213	28	6-13	4 wks	300 or 400	197	51	ADHD, either stimulant -naïve or -tolerant	Included 8 wk open label extension	2002
309	18	6-17	9 wk	170-425	131	67	ADHD without psychiatric comorbidity	Parallel group, 2:1 randomization	2004
310	17	6-17	9 wk	340 or 425 according to wt	125	64	ADHD without psychiatric comorbidity	At week 7 modafinil patients were randomized to either modafinil or pbo for final 2 wks	2004
311	24	6-17	9 wk	170-425	164	84	ADHD without psychiatric comorbidity		2004
113	1	6-13	2 wks + 2 single doses	340,425	24	-	ADHD not responding well to medication	Bioavailability assessment was main objective	2003
206	3	6-12	4 wks	100-400	20	-	ADHD without	Included optional 8 wk	2000

							psychiatric comorbidity	extension	
312	56	6-17	1 yr	170-425	536	-	Tolerated modafinil in a previous ADHD trial		ongoing

Appendix Table E. ADHD Safety and Efficacy Studies with Adderall XR included in the analysis

Protocol	No. of sites	Age range (yrs)	Duration (dys)	Dose (mg/ day)	N			Population	Comments	Study completion date
					Drug	Pbo.	Active control			
201	4	6-12	1 wk X over (5 way)	Adderall 10, Adderall XR 10,20,30	50	49	-	Current users of Adderall or MPH	Laboratory school setting	1999
301	47	6-12	3 wks	10, 20, 30 (fixed)	10 mg 129; 20 mg 121; 30 mg 124	210	-	ADHD, known to be tolerant of stimulants		2000
302	49	6-12	24 mos.	10-30	568	-	-	Participants in previous trials	Open label, long term safety	2002
303	18	≥18	4 wks	20, 40, 60 (fixed)	191	64	-	Adults with ADHD and no history of intolerance to stimulants		2002
304	18	≥18	24 mos.	20, 40, or 60	223	-	-	Adults who participated in study 303	Open label, long term safety	2005
305	365	6-12	15 wks	10-40	2968	-	-	Responders to prior stimulant treatment	Open label safety and efficacy	2002
311	27	6-17	4 wks	10, 20, 30, 40 fixed dose	237	60	-	Oppositional defiant disorder (not ADHD)		2003
312	81 (U.S., Canada)	≥18	40 wks	10-60	725	-	-	Previously treated or naive		2005
314a	50	13-17	4 wks	10, 20, 30, 40 (fixed)	258	69	-	ADHD, no special requirements		2003
314b	32	13-17	6 mos.	10-60	138	-	-	Subjects in study 314a	Long term extension of 314a	2004