

**MEMORANDUM**

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

**RCM#:** 2007-251

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**THROUGH:** Mark Avigan, M.D., C.M., Director  
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**SUBJECT:** 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review  
Drug: Modafinil (Provigil™) – schedule IV controlled substance  
Pediatric Exclusivity Approval Date: March 21, 2006

### **1. Executive Summary**

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of modafinil (Provigil) in pediatric patients. Up to the "data lock" date of 4/21/07, AERS contained a cumulative total of 1,122 modafinil-associated reports (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 3.7 % of the total (42/1122).

DDRE was asked to focus on an approximately 1-year period following the approval of pediatric exclusivity granted on 3/21/06. We used an AERS data lock date of 4/21/07, to allow time for reports received up to 3/21/07, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 132 reports (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 7.6% of the total number of cases (10/132). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

We reviewed nine unduplicated cases of various adverse events associated with modafinil during the pediatric exclusivity period, March 21, 2006 to April 21, 2007 in pediatric patients less than 17 years. One case reported death as an outcome. Additionally, we conducted a second search of AERS before the pediatric exclusivity period to identify and summarize all death cases in pediatric patients; this search did not identify any cases outside the exclusivity period. We also summarize all pertinent OSE consults with recommendations related to modafinil and a similar compound armodafinil (Nuvigil™)<sup>1</sup>, including neutropenia, hematologic disorders, hepatic disorders, serious skin events, psychiatric events, and labor and delivery disorders in this document.

Of the nine cases captured during the pediatric exclusivity period for modafinil, there was one case of a completed suicide that occurred in a 15 year old female with a history of depression. Although her attitude was recently described as “upbeat”, the event was temporal to initiation of modafinil use. It is uncertain if the natural course of her depression contributed to her suicide and based on this single case, we cannot ascertain a drug related event.

Remaining were eight non-fatal modafinil cases associated with the following (unlabeled events are underlined): social behavioral events including anger (1), worsening oppositional defiant behavior (1), suicidal ideation (1), EM (1), DRESS<sup>2</sup> (1), phimosis (1), drug-drug interaction (1), and seizure (1). There were five non- underlined events with serious outcomes that are either labeled/expected or implied in current modafinil and armodafinil labeling as relating to adults. These labeled events<sup>3</sup> have also occurred in pediatric patients in association with both drugs and have recently been identified from both clinical trial and postmarketing data. Both drug labels will adapt language into the Warnings section of the aforementioned events specifically as occurring in pediatric patients, although the drugs have no approved treatment indications for children.

There were three unlabeled events, underlined, including phimosis, drug-drug interaction, and seizure. Phimosis occurring in a newborn may likely be an idiopathic event and is a common birth defect; surgical circumcision may be required. A case of seizure is unlikely drug related because the patient did not experience a recurrence of seizure after being rechallenged with modafinil at a higher dose. The case of a drug-drug interaction with valproic acid reported a low serum level of valproic acid and the outcome was non-serious in nature.<sup>4</sup>

In conclusion, this review did not identify any serious unexpected concerns associated with modafinil in pediatric patients. However, since 2.5 to 3% of US modafinil prescriptions were filled for children 18 years old and younger between years 2002 and 2006;<sup>5</sup> and based on this level of modafinil use in the pediatric population, at this time DDRE cannot assess if the absence of a safety signal is accurate. Consequently, DDRE will continue to monitor reports of adverse events associated with modafinil in pediatric patients.

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<sup>1</sup> Armodafinil, (Nuvigil™), a single –isomer formulation of modafinil to treat excessive daytime sleepiness with narcolepsy, OSA/HS, and SWSD.

<sup>2</sup> DRESS = Drug Rash with Eosinophilia and Systemic Symptoms

<sup>3</sup> Social behavior problems including anger (1), worsening oppositional defiant behavior (1), suicidal ideation (1), EM (1), and DRESS.

<sup>4</sup> Modafinil may induce liver isoenzymes CYP 1A2, 2B6, and 3A4, while valproic acid is metabolized via the cytochrome P450 microsomal enzyme system.

<sup>5</sup> Flowers C., R.Ph., OSE Safety Review- Modafinil NDA 20-717, Serious Skin Reactions Update February 15, 2007 RCM# 2007-169

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## 1.0 Background

### 1.1 Regulatory history

#### Modafinil - (NDA 20-717)

On December 24, 1998, modafinil (Provigil™), a non-sympathomimetic stimulant by Cephalon Incorporated, was granted approval by the FDA's Division of Neurology Products (DNP) for treatment of excessive daytime sleepiness, narcolepsy.

On January 23, 2004, a supplement to the NDA 20-717 was approved for a new indication - to improve wakefulness in two patient populations with excessive sleepiness: those with obstructive sleep apnea/hypopnea syndrome (OSA/HS) and those with shift work sleep disorder (SWSD).

On December 20, 2004, Cephalon submitted another new indication supplement to NDA #20-717/S-019<sup>6</sup> for modafinil (Sparlon™) for treatment of attention deficit hyperactivity disorder (ADHD) in children under the age of 17 years. Initially, this application<sup>7</sup> (reviewed by the Division of Psychiatry Products) was granted approvable status on November, 21, 2005; subsequently, on August 3, 2006, a non-approvable status was issued because of the risk of serious skin disorders. Consequently, the sponsor withdrew their application for the pediatric ADHD indication in August 2006.

The clinical review<sup>8</sup> of Sparlon noted efficacy in the treatment of pediatric ADHD, and an approvable letter was issued on November 21, 2005; however, worrisome safety signals were also identified: (1) serious skin reactions - e.g. Stevens Johnson syndrome (SJS), (2) psychiatric adverse events, and (3) transaminase elevations. The adverse events were presented and discussed at an Advisory Committee Meeting on March 23, 2006. The Advisory panel, although they voted to incorporate labeling changes for psychiatric events, voted overwhelmingly against market approval for pediatric ADHD use because of the concern regarding modafinil-associated possible SJS, which occurred in a seven year old male who participated in clinical trials with modafinil.

#### Armodafinil - (NDA 21-875)

The Division of Neurology Products approved armodafinil (Nuvigil™) tablets, a single-isomer formulation of modafinil, to treat excessive daytime sleepiness with narcolepsy, OSA/HS, and SWSD on June 15, 2007. During the review of this application, cases of angioedema were identified. Although no cases of SJS were identified in the clinical trials, of concern were cases of hypersensitivity. Based on the safety experience in clinical trials and given the structural likeness to modafinil, labeling for armodafinil included Warnings for serious skin reactions including SJS, DRESS, and angioedema. Modafinil labeling will also be amended to reflect similar Warnings.

### 1.2 Office of Surveillance and Epidemiology (OSE) reviews of NDA 20-717 (modafinil)

OSE has performed numerous reviews on modafinil. The following is a summary of pertinent OSE reviews regarding hematologic, hepatic, serious skin, psychiatric, and labor and delivery events:

<sup>6</sup> Thomas Laughren, M.D., Director DPP; Modafinil (Sparlon™) NDA 20-717/S-019 Approvable letter, August 3, 2006

<sup>7</sup> Thomas Laughren, M.D., Director DPP; Modafinil (Sparlon™) NDA 20-717/S-019 Non-approvable letter, August 3, 2006

<sup>8</sup> Glenn B. Mannheim, M.D., Medical Reviewer DPP; Clinical Review for NDA 20-717/S-019 to treat ADHD in children (6-11 years) and adolescents (12 – 17 years)

### Hematologic disorders

On October 16, 2000, the first of three reviews of modafinil-associated neutropenia and leucopenia in patients of all ages was prepared by the Division of Drug Risk Evaluation (DDRE) that utilized AERS data. To assist with Investigational New Drug application (IND) # 59-661 for modafinil, the first review<sup>9</sup> summarized two cases of leucopenia and no cases of neutropenia. One patient required medical management and the other spontaneously recovered. There were no cases in pediatric patients (ages 0-16 years), and postmarketing monitoring continued.

Since the first review of neutropenia and leucopenia with modafinil and in anticipation of a submission of modafinil for management of ADHD, two updates of AERS cases<sup>10,11</sup> were conducted on August 11, 2003 and again on August 8, 2005. Neither update identified cases of neutropenia in the pediatric age group, ages newborn – 16 years.

For this review, we conducted another update search of AERS with a data lock date of May 21, 2007 utilizing the same criteria from previous searches to identify cases of neutropenia or leucopenia in pediatric patients ages newborn – 16 years. This search identified no cases of neutropenia or leucopenia. However, one serious case (ISR#5292729) was identified of DRESS in a 15 year old male patient who also reported a decrease in his white blood cells (WBC – 5.7). The patient recovered from all events with medical management.

### Hepatic disorders

On October 5, 2005, at the request of Dr. Glenn Mannheim, Dr. John R. Senior, M.D., reviewed a case involving a 6 year old male with vomiting and convulsions for possible hepatotoxicity. Based on the limited data in the case, Dr. Senior concluded these events were most likely the result of a viral infection and unlikely related to modafinil.

### Serious skin disorders

There are three OSE reviews<sup>12,13,14</sup> summarizing cases of modafinil-associated serious skin reactions, including SJS, that were identified in the Adverse Event Reporting System (AERS) database. The initial review, dated September 23, 2005, included a concerning case of a 7 year old male patient who experience a SJS-like serious skin rash.<sup>15</sup> Subsequent reviews identified additional cases of severe hypersensitivity reactions, including DRESS<sup>16</sup> and a compelling case of SJS in an adult female of 49 years with 50% skin involvement who required an extended stay in a hospital burn unit. The labeling recommendations were consistent amongst the reviews to include Warnings for modafinil-associated serious skin reactions and DRESS. Below are photographs of both the pediatric and adult patients, respectively, with serious skin disorders. The three full reviews will be provided upon request.<sup>17</sup>

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<sup>9</sup> Kortepeter, C., Pharm D., OSE Safety Review IND# 59-661, Modafinil associated neutropenia, leucopenia, and off-label usage for ADD/ADHD, PID# D000596, October 16, 2000.

<sup>10</sup> Flowers, C., R.Ph., OSE Safety Review, NDA 20-717, Modafinil associated neutropenia and leucopenia, email consult dated August 11, 2003

<sup>11</sup> Saini, S, Pharm.D., OSE Safety Review NDA 20 – 717, Moafinil associated neutropenia, PID# D050129, August 8, 2005.

<sup>12</sup> Flowers C. OSE Safety Review- Modafinil NDA 20-717, Serious Skin Reactions, PID#D050547 September 23, 2005

<sup>13</sup> Elekwachi, O., Pharm D. OSE Safety Review – Modafinil NDA 20-717, Serious Skin Reaction Update, PID# D060428 July 17, 2006

<sup>14</sup> Flowers C., R.Ph., OSE Safety Review- Modafinil NDA 20-717, Serious Skin Reactions Update February 15, 2007 RCM# 2007-169

<sup>15</sup> This case was re-classified as Erythema Multiforme Major (EMM) by the sponsor – same case as EM case in Executive Summary of this review

<sup>16</sup> Drug Rash with Eosinophilia and Systemic Symptoms

<sup>17</sup> Reference footnotes #9, 10, and 11.

Photograph 1. 7 year old male with modafinil assoc. SJS; AERS ISR# 4376619



Photograph 2. 49 year old female with modafinil assoc. SJS; AERS ISR# 5194832



On March 8, 2007, Dr. Lois La Grenade, Epidemiologist, reviewed portions of the sponsor's submission which the Agency had requested for NDA 20-717 (modafinil) use in ADHD.<sup>18</sup> The data, EuroSCAR study, was intended to support the sponsor's view surrounding a case of modafinil-associated serious skin reaction that was identified in a U.S. clinical study in a 7 year old male (see photo 1. above). The child reportedly received modafinil for ADHD and experienced atypical erythema multiforme major (EMM), which is contrary to the Agency's view that he experienced SJS.<sup>19</sup>

To put the study data into perspective, reporting rates were calculated comparing the observed rate of SJS/TEN in association with modafinil with the expected (background) rate. Therefore, given a case count of 4 (excluding the clinical trial case) and a projected total patient exposure of 704, 167.7 patient years in the U.S., the calculated reporting rate for modafinil

<sup>18</sup> La Grenade, L. M.D., OSE Safety Review, NDA 21-875 Review of documents submitted by sponsor re: possible association of modafinil exposure and Stevens Johnson syndrome/toxic epidermal necrolysis in response to the Agency's request for information. March 8, 2007.

<sup>19</sup> This case was re-classified as Erythema Multiforme Major (EMM) by the sponsor – same case as EM case in Executive Summary of this review

associated SJS/TEN in all ages in the U.S. is 5.7 per 1,000,000 patients as compared to the background rate of 1-2 million per patient.

Dr. La Grenade concluded that the EuroSCAR study which reported no cases of serious skin events (e.g. SJS) was insufficient for modafinil exposure to rule out an association between modafinil exposure and serious skin, SJS or toxic epidermal necrolysis (TEN). This was because EuroSCAR did not ascertain all cases of SJS/TEN, nor did it cover the entire population of the countries included in the study. She recommended that more data on the possible risk of SJS/TEN in children be studied before drug approval.

#### Angioedema and anaphylaxis

To assist DNP with their clinical review of NDA 21-875 for armodafinil (Nuvigil™), which identified cases of angioedema, we were asked to review AERS cases<sup>20</sup> of modafinil-associated anaphylaxis and angioedema. The cases of anaphylaxis were potentially confounded by other products. However, a contribution by modafinil could not be ruled out; we will continue postmarketing monitoring for similar cases. The cases of angioedema provided clinical evidence including positive rechallenges to support a possible drug association. Based on the postmarketing and clinical study cases of angioedema, labeling recommendations were made to provide Warnings for this event.

#### Psychiatric events

In a DDRE document<sup>21</sup> dated March 3, 2006, Dr. Andrew Mosholder, M.D., reviewed clinical trial data for psychiatric events including psychosis and mania, suicidal events, and aggression with all marketed ADHD drug products<sup>22</sup> including modafinil. The sponsor of modafinil was issued an Approvable Letter for pediatric ADHD at the time of his review (later the Agency issued a Nonapprovable Letter based on safety concerns; and subsequently, the sponsor withdrew their application in August 2006).

Dr. Mosholder analyzed three clinical trials, two double blind and one open label. There were no completed suicides across trials. Although the exposure to modafinil was greater, there were more events of psychosis/mania, suicidality, and aggression among the modafinil treated patients as compared to placebo.

Coinciding with Dr. Mosholder's review was another DDRE review<sup>23</sup> performed by Dr. Kate Gelperin and Ms. Kate Phelan, RPh that analyzed the same psychiatric events from postmarketing sponsor submitted and AERS data. These data were presented at the March 2006 Advisory Committee Meeting. The most important finding of this review is that signs and symptoms of psychosis or mania, particularly hallucinations, can occur in some pediatric patients with no identifiable risk factors, at usual doses of any of the drugs currently used to treat ADHD, including modafinil. The Agency has recommended label Warnings for drugs to treat ADHD in pediatrics.

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<sup>20</sup> Flowers, C. OSE safety review NDA 20-717, modafinil associated anaphylaxis and angioedema, RCM# 2007-507, March 21, 2007.

<sup>21</sup> Andrew Mosholder, M.D., M.P.H., Epidemiologist, OSE safety review, Psychiatric Adverse Events in Clinical Trials of Drugs for Attention Deficit Hyperactivity Disorder (ADHD), PID# D060163, March 3, 2006.

<sup>22</sup> Adderall XR™, Facalin™, Facalin XR™, Concerta™, Metadate CD™, Ritalin LA™, Straterra™, and Methylphenidate transdermal (MTS)™

<sup>23</sup> Kate Gelperin, M.D., M.P.H., Medical Epidemiologist, and Kate Phelan, R.Ph., OSE safety review, Psychiatric Adverse Events Associated with Drug Treatment of ADHD: Review of Postmarketing Safety Data, PID# D050243, March 3, 2006

Of note, modafinil (Provigil™) does not have an approved label indication for ADHD, and there are current Warnings for psychiatric events in adults.

### Labor and delivery

Ronald Farkas, M.D., had requested that DDRE assist with a review of armodafinil, Nuvigil™ by searching AERS for cases of intrauterine growth retardation associated with modafinil. He had identified a case in the armodafinil clinical trials. We identified one case (ISR# 4284694)<sup>24</sup> of modafinil associated intrauterine growth retardation. The baby's femur length was less than the stated gestational age and the head was in the fifth percentile but grew consistently. The baby died due to respiratory distress and severe intra-uterine growth retardation related to prematurity.

A mention of intrauterine growth retardation has been included into the pregnancy section of the armodafinil (Nuvigil™) label, and similar language will appear in the modafinil label.

## **2. Products, Indications, Pediatric Labeling, and Pediatric Filing History**

### **2.1 Provigil Products:**

Provigil™ (modafinil), NDA # 20- 717, which is sponsored by Cephalon Incorporated and approved in the U.S. on December 24, 1998, is formulated in:

Tablets: 100 and 200 mg

### **2.2 Provigil approved Indications**

Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hyponea syndrome (OSAHS), and shift work sleep disorder (SWSD).

### **2.3 Provigil Pediatric Labeling**

Currently, Provigil™ is not indicated for treatment in children.

Pertinent pediatric labeling:

**Bolded Warnings:** although the exact language has not been finalized, labeling will reflect risk identified from study and postmarketing data in adult as well as pediatric patients of the following: Serious rash including Stevens Johnson Syndrome and psychiatric symptoms. Additionally, although no specific systematic studies in pediatric patients have identified cases, there are Warnings of persistent sleepiness in adults, which may also occur in pediatric patients.

Warnings:

Psychiatric Symptoms

*Psychiatric adverse experiences have been reported in patients treated with modafinil.*

*Postmarketing adverse events associated with the use of modafinil have included mania, delusions,*

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<sup>24</sup> Flowers, C., OSE Safety Review, modafinil associated intrauterine growth retardation., 5/21/2007, RCM# 2007-1238

*hallucinations, and suicidal ideation, some resulting in hospitalization. Many, but not all, patients had a prior psychiatric history. One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of modafinil and sleep deprivation. There was no evidence of psychosis 36 hours after drug discontinuation.*

*In the adult modafinil controlled trial database, psychiatric symptoms resulting in treatment discontinuation (at a frequency >0.3%) and reported more often in patients treated with modafinil compared to those treated with placebo were anxiety (1%), nervousness (1%), insomnia (<1%), confusion (<1%), agitation (<1%) and depression (<1%). As with any psychoactive agent, consideration should be given to the possible emergence or exacerbation of psychiatric symptoms in patients treated with PROVIGIL. If psychiatric symptoms develop in association with PROVIGIL, administration consider discontinuation of PROVIGIL.*

Pregnancy: . . . Intrauterine growth retardation . . .

## 2.4 Pediatric Filing History

In response to the sponsor’s request for Pediatric Exclusivity for Provigil™, the Agency initially issued a Pediatric Written Request on 6/17/04 for studies on obstructive sleep apnea/hypopnea (OSA) and narcolepsy. A second supplement was filed, which modified the inclusion criteria for OSA by removing the requirement for studies in pediatric patients. Remaining was Cephalon’s supplemental New Drug Application (NDA# 20-717) for the treatment of excessive sleepiness associated with narcolepsy in children (ages 6-16 years). The narcolepsy study failed to provide substantial evidence for effectiveness of modafinil in the treatment of pediatric patients with narcolepsy. Nonetheless, the study will be noted in modafinil’s labeling; Pediatric Exclusivity was granted on March 21, 2006.

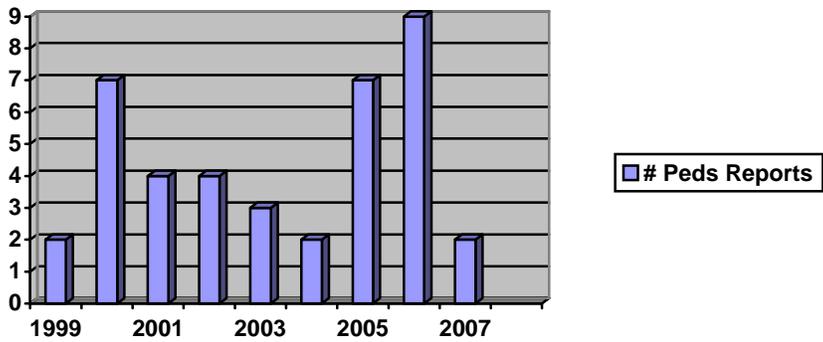
Of interest, on December 23, 2004, Cephalon submitted a supplement for attention deficit hyperactivity disorder (ADHD) in pediatric patients treated with modafinil (Sparlon™ – proposed new name). After evaluation, including an Advisory Committee Meeting on March 23, 2006, safety issues were identified (serious skin disorders), and the Agency issued a non- approval status for Sparlon™; Cephalon subsequently withdrew the application.

## 3. AERS Search Results: modafinil (Provigil™)

### 3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)

<b>Table 1: Crude counts<sup>1</sup> of AERS Reports for All Sources from Marketing Approval Date (12/24/1998 – April 21, 2007) (US counts in parentheses)</b>			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	930 ( 840)	291 (223)	33 (23)
Pediatrics (0-16 yrs.)	42 (40)	21 (19)	1 (1)

<b>Table 1: Crude counts<sup>1</sup> of AERS Reports for All Sources from Marketing Approval Date (12/24/1998 – April 21, 2007) (US counts in parentheses)</b>			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Age unknown (Null values)	149 (133)	51 (42)	10 (9)
<b>Total</b>	<b>1,122 (1,013)</b>	<b>364 (284)</b>	<b>45 (33)</b>
<small>1 May include duplicates            2 Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly. One report may indicate more than one outcome.</small>			



**Figure 1: Reporting trend for pediatric reports from approval date through the first quarter of 2007:**

**3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)**

<b>Table 2: Crude counts<sup>1</sup> of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (March 21, 2006 – April 21, 2007) (US counts in parentheses)</b>			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	96 (78)	55 (45)	10 (8)
Pediatrics (0-16 yrs)	10 <sup>3</sup> (9 <sup>4</sup> )	5 (4)	1 (1)
Age unknown (Null Values)	26 (18)	13 (9)	4 (3)
<b>Total</b>	<b>132 (105)</b>	<b>73 (58)</b>	<b>15 (12)</b>
<small>1 May include duplicates            2 Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly. One report may indicate more than one outcome.            3 Crude count. Actual count of unduplicated cases is 9.            4 Includes one duplicate report.</small>			

**4. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.**

#### 4.1 Case Characteristics:

<b>Table 3 : Characteristics of pediatric cases reported during the pediatric exclusivity period (March 21, 2006 – April 21, 2007) n=9</b>	
Gender [n= 9]	Male: 6 Female: 3
Age [n=9]	0- <1 month -1 6-11 years - 4 12-16 years - 4
Origin [n= 9]	US - 8, Foreign - 1
Event date (n=9)	2006 - 8 2007 - 1 (received: April 5, 2007)
Daily dose [n=7]	Average – 240 mg , Median – 125 mg, Range: 100 – 425 mg
Duration of therapy [n=7]	Average – 56 days , Median - 25 days Range: 3 – 240 days (8 months)
Indications [n= 8]	Attention deficit hyperactivity disorder (ADHD)/bipolar -1, ADHD/anxiety – 1, ADHD (study patients) – 2, narcolepsy – 3, “sleep disorder” - 1
Outcomes [n=9]	Death - 1, Life-Threatening, Hospitalization - 3 Disability, Congenital Anomaly -1, and Other Serious -4

#### 4.2 Summary of Cases received during the 1-year post-pediatric exclusivity period.

There were nine unduplicated pediatric cases identified in AERS for review during the designated 1-year post-pediatric exclusivity period, March 21, 2006 – April 21, 2007, including one case with death reported as an outcome. Additionally, a second AERS search was conducted to identify death cases with modafinil since its approval (December 24, 1998). This search identified one case, which was reported during the pediatric exclusivity period. The entire case series is summarized below. The unlabeled adverse events are underlined in the cases.

One fatal case (ISR# 5059015, U.S., 2006) of completed suicide was reported in a 15 year old female with a history of depression. She was prescribed modafinil for an unknown indication, and received a dose of 50 mg that was titrated up to 100 mg in seven days before completing suicide by strangulation. Concomitant medication included duloxetine, Cymbalta™, which was started in 2005, and dicyclomine (therapy dates not reported). The patient’s mother described her attitude as recently upbeat.

The remaining eight cases reported non-fatal outcomes. Although the cases may report more than one adverse event, the cases were categorized and summarized based on the prominent adverse event. The five categories describing the eight reports include: psychiatric events (3), serious skin disorders (2), congenital anomaly (1), drug interactions (1), and neurological events (1).

#### Psychiatric events (n=3)

The first case (ISR# 51298998) is a 16 year old male with a “sleep disorder” who reportedly was acting “out of character” when he experienced mental status changes including anger, defiance irrational behavior, and behavioral problems in school. The drug was stopped and the patient recovered.

The second case (ISR# 5147961) in an 8 year old male with ADHD (study patient) and oppositional defiant behavior who had no previous psychiatric hospital admissions experienced worsening behavior. The patient’s behavior included self-harm, assault on others, stealing, and physical threats. The patient was admitted to a long-term psychiatric treatment facility. Although the worsening behavior was temporal to modafinil use, the underlying disease is a possible confounder.

The third case (ISR# 5054292) of suicidal thoughts in a 13 year old female who was obese with mild depression regarding her self-image was teased about her weight by her peers. Consequently, she expressed that she wanted to “kill herself,” however after adult intervention, the patient’s emotional situation changed.

#### Serious skin disorders (N = 2)

There were two cases of serious skin disorders that reported either serious patient disability or hospitalization. Pending labeling changes include bolded Warnings for Stevens Johnson Syndrome (SJS) and DRESS<sup>25</sup>. There was one case (ISR# 5142835) in a 7 year old who experienced erythema multiforme (EM). This patient was involved in a study for ADHD and originally experience SJS; however, the diagnosis was retracted by the sponsor subsequent to much debate by multiple dermatologist, and including a public debate at an Advisory Committee meeting held in March 2006. The other patient was a 15 year old who experienced DRESS subsequent to treatment with modafinil 400 mg daily for 39 days.

#### Congenital Anomaly (n= 1)

One case (ISR# 5106356) reported from Ireland involved a Newborn who experienced phimosis, a stenosis of the preputial orifice, which will likely require circumcision. The mother discontinued modafinil at nine weeks of gestation.

#### Drug interaction (n=1)

One case (ISR#4975061) in a seven year old male reported a temporal relationship with biological plausibility of a drug-drug interaction with valproic acid, which presented as lowering of the valproic acid serum levels. No clinical outcome was reported. Modafinil may induce liver isoenzymes CYP 1A2, 2B6, and 3A4, while valproic acid is metabolized via the cytochrome P450 microsomal enzyme system.

#### Neurology event (n=1)

In one case (ISR# 4975061) a nine year old experienced seizure activity that manifested as confusion, disorientation, visual hallucinations, uncontrollable crying, slurred speech, and “unable to walk or talk” during treatment with modafinil 100 mg daily for severe narcolepsy. The patient

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<sup>25</sup> Drug Rash with Eosinophilia and Systemic Symptoms

was taken off modafinil and the symptoms persisted then the patient was enrolled into a sleep study. Modafinil was restarted at a dose of 150 mg daily and no clinical outcome was reported.

## 5. Summary/Recommendations

We reviewed nine unduplicated cases of various adverse events associated with modafinil during the pediatric exclusivity period, March 21, 2006 to April 21, 2007 in pediatric patients less than 17 years. One case reported death as an outcome. Additionally, we conducted a second search of AERS before the pediatric exclusivity period to identify and summarize all death cases in pediatric patients; this search did not identify any cases outside the exclusivity period. Moreover, we have summarized all the pertinent OSE consults with recommendations related to modafinil and a similar compound armodafinil (Nuvigil™)<sup>26</sup>, including neutropenia, hematologic disorders, hepatic disorders, serious skin events, psychiatric events, and labor and delivery disorders.

Of the nine cases with modafinil, one 15 year old female who reported as history of depression committed suicide, although her attitude was recently described as upbeat. Even though the event was temporal to modafinil use, it is uncertain if the natural course of her depression contributed to her demise. Based on this single case, we cannot ascertain that the event is drug related.

Remaining, were eight non-fatal modafinil cases associated with the following: social behavioral events including anger (1), worsening oppositional defiant behavior (1), suicidal ideation (1), EM (1), DRESS (1), phimosis (1), drug-drug interaction (1), and seizure (1). There were five non-underlined events with serious outcomes that are either labeled/expected or implied in current modafinil and armodafinil labeling as relating to adults. These labeled events<sup>27</sup> have also occurred in pediatric patients in association with both drugs and have recently been identified from both clinical trial and postmarketing data. Both drug labels will adapt language into the Warnings section of the aforementioned events specifically as occurring in pediatric patients, although the drugs have no approved treatment indications in children.

There were three unlabeled events, underlined, including phimosis, drug-drug interaction, and seizure. Phimosis occurring in a newborn may likely be an idiopathic event and is a common birth defect; surgical circumcision may be required. A case of seizure is unlikely drug related because the patient did not experience a recurrence of seizure after being rechallenged with modafinil at a higher dose. The case of a drug-drug interaction with valproic acid reported a low serum level of valproic acid and the outcome was non-serious in nature.

In conclusion, this review did not identify any serious unexpected concerns associated with modafinil in pediatric patients. We will continue to monitor reports of adverse events associated with modafinil in pediatric patients.

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<sup>26</sup> Armodafinil, (Nuvigil™), a single –isomer formulation of modafinil to treat excessive daytime sleepiness with narcolepsy, OSA/HS, and SWSD.

<sup>27</sup> social behavior problems including anger (1), worsening oppositional defiant behavior (1), suicidal ideation (1), EM (1), and DRESS.

*Concur:*

*Cindy Kortepeter, Pharm.D. 6/21/07*

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**Safety Evaluator, Team Leader**

## **Appendix I: Limitations of AERS**

### **Limitations of the Adverse Event Reporting System (AERS)**

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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/s/

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