

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-875

MEDICAL REVIEW



FDA
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF NEUROLOGY PRODUCTS

MEMORANDUM

DATE: June 2, 2007

NDA 21-875, NUVIGIL (armodafinil) tablets

FROM: D. Elizabeth McNeil, M.D., Acting Team Leader, DNDP

RE: Response to Approvable letter dated March 28 2007

I. Brief Background:

A New Drug Application for Nuvigil (armodafinil, the R-enantiomer of modafinil) was first submitted on March 31 2005. The first action letter, dated April 28 2006, was an approvable action due to safety-related concerns. The Agency was aware of a case of potential Stevens-Johnson syndrome in a pediatric participant in the study of modafinil treatment for ADHD.

A complete response was submitted by Cephalon on June 30th 2006 with subsequent submission of a major amendment on December 19 2006. The complete response and the major amendment provided data for FDA review regarding the sponsor's assessment of the risk of serious hypersensitivity reactions including dermatological manifestations such as Stevens-Johnson syndrome.

On March 27 2007, a second approvable letter was issued based upon our review of the June 2006 complete response and December 2006 amendment. In that letter, Cephalon was notified of Agency concerns/recommendations:

- “Based on the rate of serious skin and other hypersensitivity reactions with modafinil in clinical trials and the post-marketing setting, we are requesting that you adopt a bolded statement in the Warnings sections describing this risk.”
- “In addition to the bolded Warning describing the risk for serious skin reactions, we ask that you add a statement in the Warnings section describing the two apparent type I hypersensitivity reactions that were observed in armodafinil-treated patients in clinical trials.”
- “To better characterize the risk for serious skin and other hypersensitivity reactions in patients of all ages treated with modafinil and armodafinil, we recommend that you improve the follow-up of such cases in ongoing and future clinical trials of modafinil and armodafinil as well as in the post-marketing setting. Any ongoing or future studies with modafinil and armodafinil should

incorporate into the protocol a rigorous and standardized approach to the assessment and follow-up of these cases, including evaluation by a dermatologist, laboratory assessments (including complete blood counts and liver function tests), photographs, biopsy results and if applicable final diagnosis, treatment received and information regarding clinical outcome. Please propose additional strategies to minimize potential for this risk, Elements of such a strategy might include an educational component...and frequent reports of any severe rash and other hypersensitivity reactions. This plan would apply to Provigil as well.”

The most recent approvable action letter also noted that the results of the evaluation of the interactions between armodafinil and substrates of P-glycoprotein should be submitted when available along with a safety update as per 21 CFR 314.50 (d)(5)(vi)(b). The sponsor was reminded of the need for carcinogenicity studies.

II. Comments:

Cephalon agreed to the following in their complete response:

- A bolded statement in the Warnings section to describe the risk of serious rash,
- A Warning statement about the risk of angioedema
- Detailed evaluation of patients who have skin reactions during clinical trials with adverse events of rash and/or hypersensitivity “reported as a protocol-defined adverse event for expedited reporting.”
- Provision of Rash and hypersensitivity reports for Provigil and Nuvigil to the Agency quarterly. These reports will have information from clinical trials as well as postmarketing reports.
- Submission of a carcinogenicity study within 2 years

Cephalon agreed to move the section on _____
_____ in the label (teleconference held on June 8 2007).

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Serious Rash

Dr. Lourdes Villalba, DNP/DPP safety team, performed a review of the information provided in the safety update in addition to her review of the data submitted in the past related to this issue. She evaluated the available data and determined that 1585 patients under 17 years were exposed to modafinil and changed the denominator in labeling accordingly.

She found that there was “a strong signal for cutaneous and possible multi-system hypersensitivity reactions in the pediatric database,” with 13 pediatric patients in whom skin or hypersensitivity reactions had caused study discontinuation. Of those children, “12 discontinued because of a rash—alone or accompanied by fever, elevated transaminases, diarrhea or leukopenia....No such reactions were observed in placebo-treated subjects.” She recommended a change in the heading of this Warnings subsection from _____ to “serious rash including Stevens-Johnson syndrome.” She also recommended _____

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_____ I agree with these changes as I believe that they convey the appropriate information to the prescriber.

As detailed in her review, Dr. Villalba reviewed the proposal for evaluation and reporting of skin rash and or hypersensitivity reactions for clinical trials and postmarketing. She and I both found the sponsor's proposal acceptable.

She suggested that the proposed pharmacovigilance activities and educational program would be best handled through a formal RiskMap with scheduled evaluations and assessments of effectiveness of the proposed interventions. This recommendation was presented to and accepted by Cephalon on June 8 2007 during a teleconference. Cephalon will be issuing Dear Health Care Provider letters (for both Nuvigil and Provigil) to alert prescribers to the risk of serious skin reactions and angioedema.

General Safety (unrelated to angioedema, rash or multi-organ hypersensitivity)

Since initial submission of this NDA, there have been three safety updates for the armodafinil database; the first was on September 29 2005, the second was on June 30 2006, the most recent was submitted as part of the current complete response.

Dr. Ronald Farkas, a DNP medical officer, reviewed the most recent safety update. He determined that 239 patients, who all received between 100 to 250 mg/day in open-label trials, have been added to the database. The overall exposure to armodafinil is 1595 subjects; 531 have been receiving armodafinil for ≥ 12 months, 97 have been receiving armodafinil for ≥ 24 months.

While there were no deaths reported, there were 13 additional serious adverse events (SAE), none of which were dermatological or hypersensitivity related. Five of the serious adverse events described had had similar events in other patients described in the database prior to the current safety update. The eight new SAEs, which are described in detail in Dr. Farkas's review, each occurred in a single patient:

- Localized osteoarthritis
- Adenomyosis, cystocele, dysfunctional uterine bleeding, rectocele, stress incontinence, urethral disorder and uterine prolapse
- Hiatal hernia
- Intrauterine growth retardation
- Musculoskeletal chest pain, dyspnea
- Iliac artery occlusion
- Intervertebral disc protrusion

Dr. Farkas evaluated the incidence of cardiac adverse events. While 2 patients discontinued due to cardiac related adverse events and three had serious cardiac adverse events reported including an instance of myocardial infarction, these events occurred in persons who had other cardiac risk factors. Review of the cardiac events reported in this update as well as those in preceding safety updates did not provide sufficient information to attribute causality to modafinil. He recommended that patients and prescribers consider ~~_____~~ After internal discussion, a modification of this recommendation was added to labeling.

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Dr. Farkas also evaluated the incidence of hepatic adverse events, a not infrequent reason for study discontinuation. While rare elevations in transaminases were noted, no modifications are needed to the current proposed labeling.

Pregnancy

Dr. J. Edward Fisher performed the pharmacotoxicology review for this product. While I refer the interested reader to his review for the full details, I will summarize few of his key findings. These findings were reflected in his labeling recommendations:

In fertility studies, the no effect dose of modafinil in rats (240 mg/kg/day) was associated with a plasma modafinil exposure (AUC) approximately equal to that in humans at the recommended dose of 200 mg.

In studies conducted in rats and rabbits, developmental toxicity was observed at clinically relevant exposures. The higher no-effect dose for rat embryofetal developmental toxicity was associated with a plasma modafinil exposure approximately 0.5 times the AUC in humans at the recommended daily dose (RHD) of 200 mg. However, in a subsequent study of up to 480 mg/kg/day (plasma modafinil exposure approximately 2 times the AUC in humans at the RHD) no adverse effects on embryofetal development were observed.

The highest no-effect dose for developmental toxicity [in rabbits] was associated with a plasma modafinil AUC approximately equal to the AUC in humans at the RHD.

The no-effect dose for rat embryofetal developmental toxicity was associated with a plasma armodafinil exposure (AUC) approximately 0.03 times the AUC in humans at the RHD of 250 mg.

Modafinil administration to rats throughout gestation and lactation at oral doses of up to 200 mg/kg/day resulted in decreased viability in the offspring at doses greater than 20 mg/kg/day (plasma modafinil AUC approximately 0.1 times the AUC in humans at the RHD). No effects on postnatal developmental and neurobehavioral parameters were observed.

This is a marked departure from the earlier language in the modafinil (Provigil) label which while not specifically stating that the non-clinical findings are not of concern strongly implied this to be the case.

_____] The mother had a past history of clomiphene use which may or may not have been a confounder in the infant's illness. I passed this information to Dr. Farkas, who reported that he had found a case of reported IUGR in the armodafinil database. While the case that I discovered went to term and subsequently

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died of IUGR and respiratory failure, the case discovered by Dr. Farkas was electively aborted. There were a total of 9 pregnancies reported during the open-label trials of armodafinil; 5 elective abortions including the one case of IUGR, 2 normal outcomes, 2 lost to follow-up.

The labeling for NUVIGIL as well as the racemic product (PROVIGIL) has been strengthened to make prescribers and patients aware that toxicity was seen in animal models at clinically relevant doses. Armodafinil and modafinil are approved for SWSD. Since there are many women of childbearing age who work evening and night shifts, e.g. nurses as shown in the current modafinil advertising, there is a subset of the population who may be at increased risk. The initiation of a pregnancy registry would be a method to prospectively evaluate the reproductive risks of this product in humans.

Pediatrics:

While there have been studies of modafinil (PROVIGIL) in the pediatric population, there have thus far been no studies of armodafinil (NUVIGIL) in this population.

Psychiatric and nervous system disorders such as Tourettes' syndrome, insomnia, hostility, increased cataplexy, increased hypnagogic hallucinations and suicidal ideation were treatment emergent adverse events seen with modafinil use in the pediatric trials. Transient leukopenia, which resolved without medical intervention, was seen as well. Serious skin rashes, including erythema multiforme major (EMM) and Stevens-Johnson Syndrome (SJS) have been associated with modafinil use in pediatric patients though definite causality was not demonstrated. It is not known whether any or all of these findings would be seen with armodafinil use in pediatric patients.

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Clinical Pharmacology

Drug-drug interactions:

In the approvable letter, we requested the results of the evaluation of the interaction between armodafinil and substrates of P-glycoprotein. Results from an *in vitro* study were provided in this complete response and were reviewed by the Office of Clinical Pharmacology (OCP). Cephalon agreed to perform a literature search on the P-glycoprotein induction potential of armodafinil as a Phase IV commitment. OCP found the response provided by the sponsor acceptable.

Psychopharmacology:

Unlike conventional stimulants, the mechanism of action for armodafinil is not known. Compounds which are known to antagonize adverse reactions or the mechanism of actions of stimulants such as amphetamine do not have that antagonistic effect on modafinil associated actions. Dr Fisher specifically notes:

“The wake-promoting effects of modafinil, unlike those of amphetamine, were not antagonized by the dopamine receptor antagonist haloperidol in rats. In

addition, alpha-methyl-p-tyrosine, a dopamine synthesis inhibitor, blocks the action of amphetamine, but does not block locomotor activity induced by modafinil.”

While this product is scheduled, the reinforcing qualities of its psychoactive and euphoric effects should be recognized as a potential area of misuse. It is not known whether the r-enantiomer has the same or a different level of these effects. In humans, the r-enantiomer is known to have a similar effect in animals.

Recommendation:

I recommend an approval action for this product, armodafinil (NUVIGIL).

While we have concerns about serious skin reactions that may occur with armodafinil use, we may be reassured that these are rare events based upon the modafinil post-marketing experience. A review of the provided safety update did not make us aware of any additional safety signals that would warrant inclusion in labeling. We are alerting prescribers and patients to the potential risk by inserting a bolded warning for both the possibility of skin reactions including but not limited to Stevens-Johnson reactions and the risk of multi-system hypersensitivity reactions. These warnings have been accepted by the sponsor for inclusion in the product information (PI), the patient product information (PPI) and the Dear Health Care Provider letters.

The Division of Surveillance, Research and Communication Support (DSRCS) made suggestions for the PPI which have been incorporated into labeling associated with this action. I agree with the recommendation from the safety team to request Phase 4 commitments for a RiskMap as well as a pregnancy registry. The review team will take primary responsibility for monitoring of the data accrued to the pregnancy registry; the safety team will have primary responsibility for evaluating the RiskMap as well as any skin findings/angioedema.

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As we move forward with this product, we should remain aware of the potential for misuse of both armodafinil and modafinil, especially in light of its euphoric effects. We may need to reassess the evaluations of the drug abuse liability at some point if we gain evidence of significant misuse.

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/s/

Dawn McNeil
6/13/2007 02:34:55 PM
MEDICAL OFFICER

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Review of clinical data

NDA#:	NDA 21-875, NUVIGIL (armodafinil)
Sponsor:	Cephalon
Subject:	Complete Response to Approvable letter of March 28, 2007. Severe cutaneous adverse reactions and angioedema.
Material:	April 16, May 11 & May 15, 2007 submissions
Date:	June 11, 2007
Reviewer:	Lourdes Villalba, M.D., Medical Officer, Safety Team, DNP/DPP
Team leader:	Alice Hughes, MD., Team Leader, Safety Team, DNP/DPP

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1) Executive Summary

This is the third review cycle for Nuvigil (armodafinil), the R-enantiomer of modafinil (Provigil), a marketed wakefulness-promoting agent. The original Nuvigil application submitted on March 31, 2005 received an AE action on April 28, 2006, mainly because of concerns with serious skin reactions (included one case of possible Steven-Johnson Syndrome and one multi-organ hypersensitivity reaction) observed in pediatric studies with modafinil. The Provigil application for pediatric ADHD was not approved.

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A Complete Response to the AE letter for Nuvigil was submitted on June 20, 2006. Several reviews were written in reference to this Complete Response, including my review dated March 22, 2007. The application received another AE action on March 28, 2007. On April 16, 2007, the sponsor submitted a Complete Response. My current review focuses on responses pertaining to serious skin and hypersensitivity reactions and angioedema with Nuvigil (and Provigil). Other labeling issues and the Safety Update are being addressed by Dr. Farkas (OND/DNP Medical Officer).

Upon review of this Complete Response, on June 7, 2007, the FDA sent comments to the sponsor regarding its risk minimization strategies and Dear Healthcare Provider (HCP) letters for both, Provigil and Nuvigil, as well as new proposed labeling for Nuvigil. A teleconference was held between Cephalon and FDA staff on June 8, 2007, to discuss these documents. Agreement was reached on final labeling for Nuvigil and Dear HCP for both, Provigil and Nuvigil. The sponsor agreed to submit formal Risk Minimization Action Plans (RiskMAP) for both, Provigil (on July 16, 2007) and Nuvigil (3 months before launch). The sponsor also agreed to implement a Pregnancy Registry for both drugs. Both, the RiskMAP and Pregnancy Registry for NUVIGIL will be implemented upon agreement with FDA, as phase 4 commitments.

2) Review of Complete Response to the March 28, 2007 AE letter

The following review contains verbatim language from the Approvable letter (in bold font), followed by Cephalon's response and by review comments.

FDA request #1: "Based on the rate of serious skin and other hypersensitivity reactions with modafinil in clinical trials and the post-marketing setting, we are requesting that you adopt a bolded statement in the WARNINGS section describing this risk. We are also requesting that you add a WARNINGS statement describing the risk of angioedema with armodafinil."

Cephalon agreed to adopt a bolded statement in the WARNINGS section to describe the risk of serious rash and to include a WARNING statement describing the risk of angioedema with armodafinil.

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~~_____~~ Cephalon's proposed NUVIGIL labeling related to serious skin and multi-organ hypersensitivity reactions and angioedema is presented in Appendix 1.

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Comments pertaining to labeling

1.1 Discontinuations due to skin and hypersensitivity reactions with modafinil

The n=8 for the cases of rash leading to discontinuation in pediatric trials (for the *Warnings; Serious rash* section of Nuvigil labeling requested by the Division in the 3/28/07 AE letter) comes from my review of March 22, 2007, which I based on cases cited in Dr. Wilson Bryan's review of the June 30, 2007 Complete Response to the Nuvigil AE letter dated December 21, 2007. However, a previous review by Dr. Glenn Mannheim (primary reviewer for the pediatric ADHD trials), found that 26 patients had discontinued from these trials due to skin related reactions (see Appendix 2, Table from page 44 of Dr. Mannheim's September 26, 2005, review). On further review of the narratives for the 26 cases included in Dr. Mannheim's review, five of the 18 skin reactions not included in my previous review were "mild" or "moderate" skin rashes. Nonetheless, these mild and moderate rashes required discontinuation and treatment with diphenhydramine and/or corticosteroids. Therefore, they should be accounted for in the labeling as cases of rash requiring discontinuation of treatment (See Appendix 3.a). The remaining 13 cases not included in my March 22, 2007 review do not appear to be skin hypersensitivity reactions (See Appendix 3.b) or did not lead to discontinuation (Appendix 3.c).

Table 1, below, shows an updated list of cases of skin or hypersensitivity reaction that required discontinuation in the pediatric database and includes the five cases that I had not included in my previous review (*in Italics*). This table lists thirteen pediatric cases, 9M/4F, ages 6 to 12 years of age. The mean and median time to onset of the rash for these cases was 13 days (range 3 to 24 days). The dose of modafinil at the time of the reaction ranged from 100 to 425 mg daily. One case presented a clear positive rechallenge when modafinil was re-introduced at the dose of 85 mg daily.

In addition to one case of possible SJS (that the sponsor insists was atypical erythema multiforme major), twelve children discontinued because of a rash--alone or accompanied by fever, elevated transaminases, diarrhea or leukopenia. Some of these cases are consistent with early SJS or an early multi-organ hypersensitivity reaction. Eleven of the cases occurred in modafinil-treated subjects in placebo-controlled trials and 2 during open label trials. No such reactions were observed in placebo-treated subjects.

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Table 1. Cases of hypersensitivity reactions that led to discontinuation from the pediatric database.

Case ID/	Age (years) / Ethnicity/ Gender/Hypersensitivity reactions that led to discontinuation	Dose (mg/d)	Onset (day)
Rash			
#020001	12 BF, urticaria that required treatment with IV and oral corticosteroids.	225	13
#207/411	10 HM, moderate rash treated with diphenhydramine (DPH)	200	21
#08012	9 WM, moderate rash treated with DPH	200	14
#29015 <i>OL</i>	7 WM, mild rash, treated with methylprednisolone and DPH; positive rechallenge 5 days after re-starting drug 85 mg/d	340	24
#34015	6 Mixed race F, severe rash; small red lesions on arms and confluent large area on inner thighs, treated with DPH and topical hydrocortisone (preceded by upper resp. infection)	225	10
#19010	11 WM moderate rash; patient withdrew consent on day 21	300	17
Rash and some additional sign or symptom			
#062338	7 AM, rash, sore throat, fever diagnosed as SJS, or atypical EMM	425	15
#18004	8 WM, rash on cheeks, blister on lips, fever	200	14
#056180 <i>OL</i>	9 WM, petechial rash, fever, swollen eyes and elevated transaminases, considered to have a multi-organ hypersensitivity reaction.	340	13
#315	11 WF, fever, diarrhea, generalized pruritic rash, hospitalized for possible SJS later diagnosed as morbiliform rash.	200	4
#18001	6 WM, W, severe macular rash trunk & extremities, fever, vomiting, anorexia	300	3
#13011	8 WM, fever, leukopenia, abdominal pain, dry hives	100/100	?
#24004	8 WF, fever, macular rash on trunk & extremities, leukopenia	100/200	13

Gender: M=male; F=female. Ethnicity: B=Black; W=White; H=Hispanic; A=Asian. Cases in *Italics* are cases that were not included in my previous review of March 22, 2007.

On further review of the narratives of patients who discontinued from adult clinical trials with modafinil (6/30/06 submission), there were three cases in which a skin rash led to discontinuation, none of which was in placebo treated patients. They occurred on treatment Day 2 and 6 and one had an unknown onset. The cases were mild and were not accompanied by systemic manifestations. Narratives of these cases are in Appendix 4.

In summary, although only one case of possible SJS (or atypical EMM) and one multi-organ hypersensitivity reaction ended up being considered clinically relevant by the sponsor, there is a strong signal for cutaneous and possible multi-organ hypersensitivity reactions in the pediatric database. There were three cases of rash that led to discontinuation in the adult database, but the cases were mild and not accompanied by systemic manifestations.

To be consistent with CDER regulations pertaining to the cut-off for the pediatric age group, it would actually be more useful to provide information in labeling for the pediatric age <17 years, rather than <18 years. This information was requested to the sponsor and submitted to FDA on May 17, 2007, as follows:

Table 2. Patient exposure in modafinil clinical trials, by age.

Patients in Modafinil Trials by Age			
	All Placebo Controlled Trials		All Trials
	placebo	Modafinil	All Modafinil
Patients <17 yrs old	380	847	1585
Patients ≥ 17 yrs old	1339	2540	4236
Patients with missing age*	11	14	28
Total	1730	3401	5849

* Twenty-eight (28) patients from the modafinil legacy studies conducted by ~~_____~~ have age information missing.

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I assumed that those patients in the old (legacy) studies did not include pediatric patients. Therefore, the denominator for patients exposed to modafinil is **1585 for <17 years, and 4264 for adults.** It would be appropriate to include the number of patients on placebo in these trials.

An additional issue that was raised during the review of this Complete Response is that the heading for the section that describes potentially life-threatening skin and hypersensitivity reactions currently reads ~~_____~~. This heading minimizes the relevance of the reactions that have been observed with modafinil and should be changed to something more meaningful, for instance: "Serious rash, including Stevens-Johnson Syndrome" or ~~_____~~.

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1.2 Skin and hypersensitivity reactions with armodafinil as per the Safety Update (April 16, 2007)

1.2.1 Deaths:

There were no deaths related to skin or immune system disorders.

1.2.2 Serious Adverse Events:

There was one serious event of angioedema with armodafinil under the Skin and subcutaneous tissue disorders SOC (system organ class) classification during a placebo-controlled narcolepsy study. There was also a non serious hypersensitivity reaction. These cases were described in my previous review of March 2007. One case of angioedema and one hypersensitivity reaction (that included bronchospasm) in a small database is of concern. The sponsor has agreed to include angioedema in the WARNINGS section of the labeling.

1.2.3 Discontinuations due to Adverse Events:

Discontinuations due to skin and immune system disorders in the armodafinil database are presented in Table 3. Narratives of cases in which rash led to discontinuation are presented in Appendix 5.a.

Table 3. Adverse events causing discontinuation from the Immune System and Skin and Subcutaneous Tissue disorders MedDRA System Organ Classes (SOC), as presented by the sponsor.

SOC MedDRA PT	Placebo-controlled studies		All studies
	Armodafinil 150 & 250 mg/d N= 645 n (%)	Placebo N= 445 n (%)	Armodafinil 150 & 250 mg/day N= 1516 n (%)
Immune system disorders	0	0	1 (<1)
Hypersensitivity			1
Skin and subcutaneous tissue disorders	6 (<1)	4 (<1)	10 (<1)
Rash	2	-	4
Alopecia areata	-	-	1
Angioneurotic edema	1	-	1
Hyperhidrosis	1	-	1
Psoriasis	-	-	1
Rash papular	1	-	1
Urticaria	1	2	1
Rash macular	-	1	1
Skin odor abnormal	-	1	0

Source: Safety Update, April 16, 2007, Complete Response, Summary 4.6.2 & 4.6.3. Patients are counted only once in each preferred term category and only once in each system organ class category

Of the PT terms in Table 3, the following terms could be grouped under the category “skin rash”: rash, rash papular, rash macular and urticaria (grouped in this way, 4 [0.6%] of these adverse events occurred in the Nuvigil group vs. 3 [0.7%] in the placebo group). These rashes were not serious but nevertheless led to discontinuation. Of note, of the 3 placebo cases listed by the sponsor, the “macular rash” was actually a “hyperpigmented skin lesion on the left cheek” and one of the urticaria cases started prior to entering the study. Therefore, the number of skin rashes leading to discontinuation is *five* on armodafinil (4 in placebo-controlled trials and one in an open label study) and *one* on placebo.

The narratives of cases described above are consistent with other narratives/CRFs presented by Cephalon in the past, in which a detailed description of the rash is missing. As per the current Complete Response, the sponsor will adopt specific procedures for patients who discontinue from clinical trials due to a skin rash and/or hypersensitivity reactions.

In addition to the patients described above, who discontinued due to an adverse event of skin rash, three patients who discontinued due to other reasons also had a skin rash (See Appendix 5.b). Of these, patient 036001 developed a skin rash, described as a very mild erythematous rash (suboccipital, neck/ shoulders) on Day 47 of armodafinil treatment. Elevated liver enzymes were detected on day 57 (there were no additional labs between screening and day 57), which was the stated reason for discontinuation. Apparently no hematologic abnormalities (such as leukopenia or eosinophilia) or vital signs abnormalities (such as fever) were reported during the study. The mild rash and elevated liver enzymes may have started to develop at the same time. Both improved after drug discontinuation. By day 105, Alkaline Phosphatase was still somewhat elevated but ALT, AST and GGT were back to normal; the rash had not resolved completely.

In my opinion, this could have been the beginning of a multi-organ hypersensitivity reaction that was caught in time; however, there is not sufficient information to confirm this diagnosis.

1.2.4 Common Skin and Immunologic system disorder Adverse Events:

MedDRA Preferred terms with an incidence of at least 2% within the Skin and Subcutaneous Tissue disorders SOCs were Rash and Dermatitis. However, there were other PT terms within this SOC that could be grouped within the category “rash.” (Table 4).

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Table 4. Incidence of skin rash-related events in armodafinil studies

	Placebo-controlled studies		All studies
	Armodafinil 150 & 250 mg/d N= 645 n (%)	Placebo N= 445 n (%)	Armodafinil 150 & 250 mg/day N= 1516 n (%)
RASH	16 (2.5)	3 (0.2)	60 (4.0)
Rash	13	1	49
Heat rash	-	-	4
Rash papular	1	-	2
Rash vesicular	-	-	2
Rash erythematous	-	-	1
Rash macular	2	1	2
Rash pruritic	-	1	-
DERMATITIS	8 (1.2)	2 (0.5)	28 (1.9)
Dermatitis contact	7	2	20
Dermatitis	1	-	2
Dermatitis allergic	-	-	4
Dermatitis acneiform	-	-	1
Dermatitis exfoliative	-	-	1
URTICARIA	4 (0.6)	4 (0.9)	10 (0.7)
Urticaria	3	4	9
Urticaria contact	1	-	1

Source: Summary 4.1.1 and 4.1.3, April 16, 2007 Complete Response, Safety Update. Patients are counted only once in each preferred term category and only once in each system organ class category.

Table 4, shows adverse events that included the word “rash”, “dermatitis” or “urticaria” in armodafinil studies. The incidence of rash (any event that contained the word rash) in placebo-controlled studies was 2.5% for armodafinil and 0.2 % for placebo; in all studies, including the open label studies, the incidence was 4%.

The incidence of dermatitis-related events was also higher in the armodafinil group (1.2%) as compared to placebo (0.5%). It is unclear how the diagnosis of “dermatitis” was made, and whether it was correct or not.

A table with all adverse events pertaining to the MedDRA SOC Skin and Subcutaneous (S/C) Tissue disorders and Immune System disorders is presented in Appendix 6. Of note, there were 15 “hypersensitivity” reactions under the Immune System Disorders SOC, among 1516 patients who received armodafinil. The term “hypersensitivity” is vague and does not convey which kind of hypersensitivity the patient had. Additionally, two patients had facial swelling, in addition to the case of angioedema. Hypersensitivity reactions, (including multi-organ hypersensitivity) and angioedema will be under the WARNINGS section of labeling.

1.2.5 Skin and Immunologic System disorder AE by age, gender and race.

Review of adverse events under the Skin and S/C Tissue disorders and Immunologic System disorders by dose, age, gender and race does not point out to specific risk factors.

The data suggest that there may be an increased incidence of rash related events in Non-White patients, but the numbers are too small for definitive conclusions. The incidence of rash-related events (rash, rash papular, rash macular, rash pruritic) in the placebo-controlled trials was 1.4% and 6.1 % for armodafinil-treated White and Non-white patients, respectively, and 0.6% and 1.2 % for placebo-treated White and Non-white patients, respectively. However, the incidence of rash-related events (rash, heat rash, rash papular, rash erythematous, rash macular, rash vesicular) in the "All studies" dataset was 3.8% and 4.1% for armodafinil-treated White and Non-White patients, respectively.

1.3 Multi-organ hypersensitivity reactions

The Safety Update included as part of the Complete Response of April 16, 2007 includes patient 036001, who could have been developing a multi-organ hypersensitivity reaction, but there is limited information to make this diagnosis (see full narrative under section 1.2.3).

Based on the multi-organ hypersensitivity reactions observed with modafinil, [REDACTED] [REDACTED] However, given its clinical seriousness and for a more logical presentation of the information, the description of the multi-organ hypersensitivity reactions belongs to the WARNINGS section of labeling. [REDACTED]

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Additionally, the bolded WARNING describing serious rashes in the pediatric studies mentions one "[REDACTED]" For consistency, the term "[REDACTED]" should be changed to "multi-organ" hypersensitivity reaction.

b(5)

1.4 Angioedema

One case of serious angioedema, one hypersensitivity reaction with bronchospasm and two cases of facial swelling were observed in the NUVIGIL clinical studies. Cephalon has accepted a statement about angioedema in the WARNINGS section of labeling for NUVIGIL. In a separate submission to NDA 20-717 (Provigil [modafinil]) that is being reviewed by Dr. Farkas, Cephalon has not included a WARNING statement for angioedema. A review of postmarketing reports of angioedema in association with modafinil in AERS conducted by OSE/DDRE on March 23, 2007, found ten cases of angioedema (HLT MedDRA term) temporarily related to modafinil, four of which required discontinuation and immediate medical intervention. At a teleconference held on April 3, 2007 the DNP asked Cephalon to make the PROVIGIL labeling consistent with that of NUVIGIL. Although the risk of angioedema does not rise to the level of the ACE inhibitors or NSAIDs, for consistency with NUVIGIL, the DNP safety team recommends

that the term angioedema be added to the WARNINGS section of the PROVIGIL labeling.

1.5 Summary of findings/recommendations regarding labeling

- On further review of the cases of discontinuations due to skin hypersensitivity reactions with modafinil for children there are more cases than the number initially proposed by FDA [final numbers 13/1585, as compared to 0 among 380 placebo]. Although characterized as “mild to moderate,” the new cases nonetheless required discontinuation and treatment with diphenhydramine and/or topical or systemic corticosteroids, and therefore should be included in labeling. The median time to onset of these skin reactions was 13 days, which should also be included.
- No serious rashes occurred in adult trials with modafinil; however, there were three discontinuations due to non-serious skin rashes with modafinil and none on placebo.
- No serious rashes occurred in adult trials with armodafinil; however, there were five discontinuations due to non-serious rashes, vs. one with placebo.
- The language regarding multi-organ hypersensitivity reactions should be under WARNINGS instead of PRECAUTIONS
- Angioedema should be a WARNING for PROVIGIL as well as NUVIGIL.

The newly proposed labeling pertaining to rash and hypersensitivity reactions for both Nuvigil and Provigil is as follows:

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Additionally, some language should cross-reference the PEDIATRIC USE section to the WARNINGS for serious skin and hypersensitivity reactions in pediatric clinical trials.

FDA request #2. “To better characterize the risk for serious skin and other hypersensitivity reactions in patients of all ages treated with modafinil and armodafinil, we recommend that you improve the follow-up of such cases in ongoing and future clinical trials of modafinil and armodafinil, as well as in the postmarketing setting.”

- Cephalon agrees to thoroughly evaluate skin rash and hypersensitivity reaction in all Cephalon-sponsored clinical studies with modafinil and armodafinil. Any adverse event of skin rash or hypersensitivity reaction will be reported as a protocol-defined adverse event for expedited reporting. For this event, the investigator must fully evaluate the patient according to the following procedures:
 - (a) Instruct the patient to immediately discontinue use of the study drug.
 - (b) Have the patient in for an unscheduled visit to perform a full evaluation, including the full review of body systems.
 - (c) Record history and time course of the event, obtain digital photographs of the affected areas, and complete the protocol-defined adverse event for expedited reporting (PDEAE) form and the skin rash and hypersensitivity reaction page of the case report form (CRF).
 - (d) Contact the Cephalon study medical monitor immediately. Following a joint review of the case, a determination will be made regarding whether the patient should receive a dermatologic consult or other medical referral. Dermatologic consult will be arranged for all rashes with systemic features, all rashes thought to be drug related, and for other rashes at the request either of the principal investigator or medical monitor. Dermatologic evaluation should occur within 48 hours of the request for a consult. The need for other medical referrals will also be determined at this time.
 - (e) Additional laboratory investigations, including a complete blood count with differential, liver and renal function tests, and urinalysis, will be performed for any patients with systemic features or as deemed clinically appropriate by the investigator or medical monitor.
 - (f) If a rash is determined not related to study drug treatment (e.g., reaction to poison ivy, heat rash), study drug may be restarted at the discretion of the investigator with the agreement of the medical monitor.
 - (g) If a dermatologic consult is required, the evaluation will consist of a thorough examination and will always include photographs. A biopsy of the affected area will be performed, if deemed appropriate by the dermatologist. At the conclusion of this examination, the dermatologist will provide a complete report to the investigator. After completion of the evaluation of the skin rash, if it is determined not to be drug related, the patient, the investigator, the medical monitor, and the dermatologist must be in agreement regarding the patient restarting treatment with the study drug.
 - (h) The investigator will submit any additional information, including a dermatologic evaluation (when conducted), as an addendum to the original form completed for the protocol-defined adverse event for expedited reporting, to Cephalon making certain to record the final diagnosis, treatment, and outcome.
 - (i) Patients with a suspected hypersensitivity reaction will not recommence study drug.
- All reports of skin rash or hypersensitivity reaction received from any source (ie, clinical studies or spontaneous reports), and subsequent follow-up information, regardless of seriousness or severity, will be processed as expedited (15-day) reports to the FDA using a MedWatch form (FDA Form 3500A).

Comment: Cephalon's proposal for evaluation of all adverse events of skin rash or hypersensitivity reaction with expedited reporting and the proposed follow up for clinical studies and postmarketing reports is acceptable.

FDA Request #3: “Please propose additional strategies to minimize the potential for this risk. Elements of such a strategy might include an educational component (including statements that armodafinil is not approved for use in pediatric patients), and frequent (e.g., quarterly) reports of any severe rash and other hypersensitivity reactions. This plan would apply to Provigil as well.”

Processes to minimize the potential for risk associated with the use of PROVIGIL and NUVIGIL will include a pharmacovigilance program and an educational program.

- Pharmacovigilance program:

On a quarterly basis, Cephalon will submit to the FDA an analysis and line listing of all expedited reports of skin rash or hypersensitivity reaction related to the use of PROVIGIL and NUVIGIL that were provided to the agency within that quarter.

Comment: The proposal pertaining to the serious skin and multi-organ hypersensitivity reactions is acceptable. However, the issue of _____ use needs to be better addressed. The sponsor should submit all postmarketing adverse reactions that occur _____ as expedited reports and provide regular reports to FDA on _____ and actions they have plan to take or have taken to discourage _____ Prevention of _____ would be better achieved through a formal RiskMAP.

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- Educational program:

Cephalon states that the main objective of the educational program will be to communicate the important risk information for PROVIGIL and NUVIGIL, including the warnings about serious rash and other hypersensitivity reactions. The key messages are supposed to include the following:

- If a patient does experience a rash, the patient should discontinue use and immediately call their physician.
- If a physician receives a report of skin rash or hypersensitivity reaction, the physician should notify Cephalon immediately.
- PROVIGIL and NUVIGIL are not approved for use in pediatric patients.

Major elements of the educational program are provided in Table 2

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Table 2. Educational Program for PROVIGIL and NUVIGIL

No.	Intervention/Tool	Description	Audience	Timing
1	Prescribing information	Will contain warnings/precautions for serious rash and other hypersensitivity reactions	HCPs	PROVIGIL within 180 days postapproval of the final labeling NUVIGIL at the time of product launch
2	Medication guide or PPI	Dissemination of product information including warnings/precautions for serious rash and other hypersensitivity reactions	Patients	PROVIGIL within 180 days postapproval of the final labeling NUVIGIL at the time of product launch
3	Dear HCP letter (see Appendix A)	Dissemination of letter to inform HCPs of warnings/precautions for serious rash and other hypersensitivity reactions; audience to receive letter will be broad-based and include HCPs, pharmacists, drug compendia, and MCOs.	HCPs, pharmacists, drug compendia, MCOs	PROVIGIL immediately postapproval of final labeling NUVIGIL at the time of product launch
4	HCP-specific promotional materials	Will contain appropriate fair balance including warnings/precautions for serious rash and other hypersensitivity reactions	HCPs	PROVIGIL within 180 days postapproval of the final labeling NUVIGIL at the time of product launch
5	Product-specific patient education and promotional materials	Will contain appropriate fair balance including warnings/precautions for serious rash and other hypersensitivity reactions	Patients	PROVIGIL within 180 days postapproval of the final labeling NUVIGIL at the time of product launch
6	Pharmaceutical compendia	Updated product information, including warnings/precautions for serious rash and other hypersensitivity reactions will be sent to the major drug compendia.	Pharmaceutical compendia	PROVIGIL within 30 days postapproval of the final labeling NUVIGIL at the time of product launch
7	Scientific exchange via Cephalon Professional Services Medical Information	Appropriate standard response letters will include warnings/precautions for serious rash and other hypersensitivity reactions.	HCPs	PROVIGIL within 30 days postapproval of the final labeling NUVIGIL at the time of product launch
8	Field representative training	Product-specific field representative training covering the approved prescribing information will include the warnings/precautions for serious rash and other hypersensitivity reactions.	Field representatives	PROVIGIL within 60 days postapproval of the final labeling NUVIGIL at the time of product launch

HCP=health care professional; MCO=managed care organization; PPI=patient package insert.

Source: April 16, 2007 submission.

All risk minimization activities pertaining to NUVIGIL will start at the time of product launch, whereas for PROVIGIL, some activities will start immediately (Dear HCP letter), and others will start within 30 days (communication to Pharmaceutical compendia and to HCP via Cephalon Professional Services Medical Information), 60 days (field representative training) or 180 days of final labeling approval (labeling, PPI, HCP and patient specific educational materials).

1. Prescribing information

Provided that the sponsor agrees with the labeling proposed by FDA, it appears that 180 days to implement the new labeling for PROVIGIL is too long. A CBE should not take that long to be implemented.

2. PPI

As part of the patient directed educational program, the sponsor has submitted a draft MedGuide and a patient package insert (PPI), both documents with similar content and format. The DNP decided that a PPI could be adequate to address this safety issue. The PPI was reviewed by OSE (DSRCS). Several edits were made in order to enhance the understanding and ability of patients to identify serious adverse reactions associated with the use of NUVIGIL. DSRCS' proposed language will be attached to the action letter.

3. Review of Dear Healthcare Provider letters

Letters to communicate the important risk information for PROVIGIL and NUVIGIL, including the warnings about serious rash and other hypersensitivity reactions, will be sent to the following healthcare professionals:

- Physicians (would-be prescribers in the case of PROVIGIL and groups of physicians in the case of NUVIGIL) from the following specialties: sleep medicine, neurology, pulmonology, primary care providers, and others
- Pharmacists (with Cephalon's internal database covering the majority of practicing pharmacists from national and regional retail chains)
- Drug compendia: American Society of Health-System Pharmacists (ASHP), USP DI, Drugdex (Micromedex), Drug Facts and Comparisons, First Databank
- Medical information organizations: WebMD and Epocrates

Comment: It is unclear who exactly will be the target of the healthcare professionals.

The Dear HCP letters for NUVIGIL and PROVIGIL submitted by the sponsor on 4/16/07 are provided as follows, with edits by the DNP Safety Team. Sentences to be added are underlined, and those to be deleted are ~~stricken through~~

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4. HCP specific promotional materials

The sponsor plans to have product specific patient education and promotional materials that will contain “appropriate fair balance including warnings/precautions for serious skin rash and other hypersensitivity reactions.”

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5. Product-specific patient education and promotional materials

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6. Pharmaceutical compendia

Updated information of warnings/precautions regarding serious rash/hypersensitivity reactions will be send to the major drug compendia.

No details are provided. Acceptability of this strategy as an education tool depends on the final language adopted by the sponsor.

7. Scientific exchange via Cephalon Professional Services Medical information.

Standard response letters will include warnings/precautions for serious rash and other hypersensitivity reactions. An example of NUVIGIL and PROVIGIL standard response letters [Occurrence of dermatologic adverse events coincident with the use of NUVIGIL] and product summaries (which will be distributed with all standard response letters) were included in the submission.

The response pertaining to the occurrence of dermatologic adverse events includes a first page which uses verbatim language from the labeling, and a section called "General Considerations, as follows:

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If your inquiry about the safety profile of this Cephalon product involves an actual adverse reaction, please complete the attached "Adverse Event Worksheet" form and return it to Cephalon for immediate processing.

As noted in the cover letter, NUVIGIL is indicated to improve wakefulness in patients with ES associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder. In OSAHS, NUVIGIL is indicated as an adjunct to standard treatment for the underlying obstruction.

Comment: These standard letters include information from the serious skin reactions but do not include information on multi-organ hypersensitivity reactions and angioedema. The Product Summary for NUVIGIL/PROVIGIL mention part of labeling but do not specifically mention that SJS, TEN and DRESS have been reported with modafinil.

8. Field representative training

The Field representative will be trained on the approved prescribing information related to serious rash and multi-organ hypersensitivity.

Comments to the proposed risk minimization strategies:

In response to FDA request #3, the sponsor's proposed risk minimization strategies include a pharmacovigilance plan and an educational plan. The proposed pharmacovigilance plan is acceptable. However, the educational materials directed to physicians and consumers consistently minimizes the risk of life-threatening skin and multi-organ hypersensitivity reactions with PROVIGIL and NUVIGIL, by referring to _____ throughout the material, omitting to mention the terms SJS, TEN and DRESS. b(4)

The consumer directed education and promotional material does not provide much education in terms of risks of serious adverse reactions and potential for abuse. The Office of Surveillance and Epidemiology, DSCRS, has specific edits to the proposed PPI. The patient educational material should be consistent with the information presented in the edited PPI.

The word "rare" referring to postmarketing AEs of serious skin reactions is acceptable in the context of describing the frequency of cases of SJS, TEN, DRESS, and other serious multi-organ hypersensitivity reactions, but should be removed from broader descriptions of skin-related adverse events including rashes leading to discontinuation in pediatric clinic trials, as this broader subset of all skin-related adverse events in pediatric clinical trials was not rare.

Some of the promotional materials omit to specifically mention SJS, TEN and DRESS as part of the "Fair Balance" statement. Additionally, some pieces do not mention psychiatric symptoms. None of the pieces mentions the potential for abuse, which I believe should be included in "Fair Balance" statements. Of note, DDMAC has not reviewed the promotional materials. DDMAC may have additional comments at the time it reviews the promotional materials.

The issue of pediatric off-label use needs to be better addressed. PROVIGIL was not approved for use in Attention Deficit Hyperactivity Disorder in the pediatric population because the risks outweighed the benefits associated with its use. Of particular concern was one case of possible Stevens-Johnson syndrome and one multi-organ hypersensitivity reaction among 1000 patients enrolled in modafinil pediatric clinical studies. _____ b(4)

_____, prevention of off-label pediatric use for PROVIGIL and NUVIGIL is of paramount importance. It is unclear whether the target audience will appreciate that PROVIGIL and NUVIGIL are not recommended for the pediatric population. An appropriate sentence throughout b(5)

the educational and promotional material for NUVIGIL would be: "Armodafinil has not been studied in pediatric patients in any setting and is not approved for use in pediatric patients for any indication." An appropriate sentence for PROVIGIL would be:

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Upon review of Cephalon's proposed risk minimization strategies, the Safety Team recommends that in order to effectively reduce the risk of serious skin and multi-organ hypersensitivity reactions, but more importantly, to reduce off-label pediatric use, both NUVIGIL and PROVIGIL would benefit from a formal Risk Minimization Action Plan (RiskMAP). For completeness, the sponsor should submit a full RiskMAP, incorporating the comments provided above, as soon as possible. This is acceptable as a phase 4 commitment.

3) Negotiations with the sponsor

A teleconference was held between Cephalon and FDA staff on June 8, 2007 to discuss final labeling, Dear HCP letters and the FDA proposed RiskMAP. Minor changes were made to the FDA proposed label and Dear HCP letters. The sponsor agreed to submit RiskMAPs for both, PROVIGIL (July 16, 2007) and NUVIGIL (3 months before launch). The sponsor also agreed to implement a Pregnancy Registry. Both, the RiskMAP and Pregnancy Registry for NUVIGIL will be implemented upon agreement with FDA as phase 4 commitments.

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Appendix 2. Skin Lesions Identified in the Vignettes of Subjects Leaving the Pediatric ADHD Trials Because of an Adverse Event (from page 44 of Dr. Mannheim's review)

Study	Pt No	Age	Sex	Race	Dose	SAE	WAE	Event
207	315	11	F	W	100 mg	X		Turners on somatotropin, DDAVP; fever, abdominal pain, diarrhea X 9days; gen. pruritic <u>maculopapular (morbilliform) rash</u> ; ? SJ
	411	10	M	H	100 mg		X	Rash; suicidal ideation, disruptive, aggressive, non-compliant behavior
207 DB	405	7	M	H	200 mg	X		Rash week 1; disruptive behavior week 3-4; abnormal ECG (U waves); <u>suicidal ideation</u>
	18001	6	M	W	300/0 mg		X	Mild HTN, <u>anorexia</u> , severe <u>rash</u> , fever, vomiting, <u>weight decrease</u> (loss)
	8012	9	M	W	200/100 mg		X	Moderate rash
	18004	8	M	W	200/100 mg		X	<u>Fever, vesiculobullous rash</u> on cheeks with severe blisters on lips; insomnia
	13011	8	M	W	100/200 mg		X	<u>Leukopenia</u> , abdominal pain, nausea, fever, dry hives
	20005	10	M	W	100/200 mg		X	<u>Insomnia</u> , irritability (<u>nervousness</u>), increased labile mood, verbal tic; abdominal pain, nausea, strept throat, fever, rash
	24004	8	F	W	100/200 mg		X	Severe rash, leukopenia
309	19137	10	F	W	255 mg		X	URI, pharyngitis followed by weight loss, indigestion (dyspepsia), rash, <u>headache</u> , <u>fever</u> , tremor, panic attacks (agitation).
	31149	8	F	Brazilian	340 mg		X	Irritability (<u>nervousness</u>), amblyopia, headache, insomnia, dry mouth, confusion, pruritus, conjunctivitis
311	42309	8	M	W	425 mg	X		Fever, vomiting, nausea, rash, dehydration, abdominal pain; diagnosed with duodenal ulcer, <u>duodenitis (peptic ulcer)</u> with spasm (<u>hypertonia</u>); sweating, insomnia, night terror (abnormal dreams), functional heart murmur
	62338	7	M	Asian	340 mg		X	Insomnia, fever, sore throat; rash over entire body, extensive skin peeling; moderate skin blistering; burning on urination; upper and lower lips (<u>Steven Johnson Syndrome</u>); <u>erythema multiforme</u> by history, and SJ by definition
	48361	10	F	W	170 mg		X	Possible allergic reaction; dystonic (<u>dystonia</u>) reaction
	49327	10	F	W	425 mg		X	Palpitations, moderate <u>tachycardia</u> , amblyopia, flushed face (vasodilatation)
	48017	9	M	W	425 mg		X	Knee contusion, plantar warts (benign skin neoplasm); severe <u>pneumonia</u> (i.v. antibiotics) followed later by moderate sinusitis
312	58006	6	M	H	425 mg	X		Abdominal pain, constipation, alopecia, rebound inattention (abnormal thinking), ringworm (fungal dermatitis); followed 3.5 months later by strept throat, emesis, <u>dehydration</u> , ketoacidosis, hypoglycemia
	2007	9	M	B	425 mg		X	Exacerbation of <u>headache</u> ; blotches on tongue (tongue disorder), presumptive strep throat;

3016	10	M	W	425 mg	X	gastroenteritis Varicella (Herpes zoster) week 2, followed at 5.5 months by movement disorder (<u>dystonia</u>)
29015	7	M	W	340 mg	X	Rash day 24, treated with prednisone + Benadryl; drug stopped X 10 days, restarted at day 34 at 85 mg, with return of rash (positive rechallenge)
31007	9	M	W	255 mg	X	Dry, reddened lips (dry mouth); <u>insomnia</u>
34004	7	M	W	340 mg	X	Pharyngitis; <u>insomnia</u> x 3 weeks; dyspepsia; strept throat; hostility; dry mouth; headaches
34007	12	M	B	425 mg	X	Eczema; pharyngitis at day 164 followed by GGT increase to 3.5 X ULN [77: 3-22]; drug stopped at day 189; GGT decreased to 2.6 ULN [57] at day 196; <u>gamma-glutamyl transpeptidase increased</u>
49017	6	M	W	340 mg	X	Worsened allergies (allergic reaction) X 26 days; worsening <u>insomnia</u>
56003	9	W	M	340 mg	X	<u>Fever</u> , generalized body hives (<u>urticaria</u>), swollen eyes (<u>facial edema</u>), <u>vomiting</u> on day 13 resulting in stopping drug; on day 14, ALT elevation to 17.2 times ULN: 517; 0-41) and AST elevation to 10 times ULN ; 409; 0-41), resolving by day 48 to 29 and 28 U/L, respectively.
57006	7	W	M	425 mg	X	Increased appetite X 35 days; persisting insomnia; URI (infection), day 22 X 2 weeks; treated with Benadryl on day 23, ? duration and reason; decrease self esteem (personality disorder); <u>emotional lability</u>

No Placebo Cases

SAE=Serious Adverse Event; WAE=Adverse Event Leading to Withdrawal

XXX= Adverse Event Term Identified By Sponsor

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Appendix 3. Skin reaction that led to discontinuation in pediatric ADHD studies.

3.a – Narratives of pediatric cases in which a skin hypersensitivity reaction led to discontinuation included in my March 22, 2007 review.

#020001 12 year-old female, developed urticaria requiring treatment with IV and oral corticosteroids.

#24004, 8 year old white female, presented fever, macular rash on trunk and extremities, and leukopenia.

#062338, 7 year-old Asian boy enrolled a pediatric ADHD study protocol for modafinil. Fifteen days after the first dose of study medication, the patient reported a sore throat and a temperature of 101.9 degrees Fahrenheit, symptoms were consistent with streptococcal pharyngitis or Coxsackie viral infection. Additionally, there was a small rash on several areas on his body. The patient developed a significant severely itchy skin rash that involved most of his body. His lips were swollen, red and crusty, and he had difficulty urinating due to pain. This case was extensively discussed at the Psychiatric Drug Advisory Committee and thought to be a possible case of SJS. The sponsor sustains that this case was atypical Erythema Multiforme Major.

#18004, 8 year old boy had a moderate rash on the cheeks and severe blisters on his lips. The study drug was discontinued and the rash resolved. Additional description of the rash was not provided. The narrative does not include sufficient information for a more definitive assessment. This case was reviewed at the March 23, 2006 Psychiatry Drug Advisory Committee and assessed as unlikely to be SJS.

#056180 OL (also listed as subject 056003) had fever, swollen eyes and general body hives, associated with elevated alanine aminotrasferase and aspartate aminotransferase. The rash was petechia-like not maculopapulous, on the cheeks and all four limbs and the abdomen.

#315, 11 year-old female had a generalized rash on the face and chest and was hospitalized with a provisional diagnosis of Stevens-Johnson Syndrome. The subject was examined by a dermatologist who determined that this was a “moderate morbiliform rash” and not SJS. There was no mucosal involvement and the rash resolved within a week. This was a serious event. This case was reviewed at the March 23, 2006 meeting of the Psychiatry Drug Advisory Committee and assessed to be unlikely to be SJS.

#18001, 6 year-old white boy had a severe “macular” rash on the truck and extremities, associated with mild decreased appetite, fever, vomiting, and weight loss. The study drug was discontinued and the rash resolved after 15 days. There is no report of mucosal involvement or hospitalization. The narrative does not include sufficient information for a more definitive assessment.

#13011, 8 year-old female developed leukopenia, abdominal pain and dry hives

3.b- Narratives of pediatric cases in which a skin hypersensitivity reaction led to discontinuation which I had not included in my March, 2007 review

#207/411 10-year-old Hispanic boy with ADHD. The patient received 200 mg/day of PROVIGIL during the first treatment period (20 July through 27 July 2000), followed by the placebo during the second treatment period (days 8 through 14, ending 3 August 2000), and 100 mg/day of PROVIGIL during the third treatment period (days 9 through 21, ending 9 August 2000). At the week-1 LSP day (27 July 2000), the patient expressed a suicidal statement to the counselor. On day 21 (10 August 2000), the patient reported having a rash (itchy rash of forehead and scalp). Study drug was discontinued the same day, and Benadryl (37.5 mg) was administered orally (for 1 day). Clinical laboratory evaluations were completed a week later (day 28), and the physical examination and ECG were performed 2 weeks later (day 35). The rash resolved by day 35 (24 August 2000; 2 weeks after discontinuing study drug) with no residual effects.

#08012 – 9 year old white boy with ADHD began treatment with PROVIGIL 200/200mg on 25 April 2002. He took study drug for 14 days, and his last dose was taken on 8 May 2002. On May 6 2002 an adverse event of moderate rash was reported for this child. The boy was treated with diphenhydramine, study drug was discontinued on 8 May 2002 and the boy was withdrawn from the study. The event resolved with no residual effect.

#29015 OL - Patient 029015, a 7-year-old white boy with a diagnosis of ADHD, began treatment in the open-label study with 85 mg/day of modafinil on 22 April 2004; his dosage of study drug was titrated to 340 mg/day on study day 10. He had previously taken placebo in double-blind study C1538d/310/AD/US. He had a prior history of allergy to penicillin (rash) and was receiving no concomitant medication at the time of entry to the open-label study. On study day 24, the patient experienced mild rash, considered by the investigator to be possibly related to treatment with study drug, and was treated with methylprednisolone acetate and diphenhydramine hydrochloride. Study drug was interrupted because of the rash between days 26 and 33; the rash resolved with no residual effect on study day 29. Study drug was restarted at 85 mg/day on study day 34 and the rash returned that same day. It was mild in intensity and considered by the investigator to be definitely related to treatment with study drug. The patient's last dose of study drug was on study day 34, and the rash resolved with no residual effect on study day 39. The patient was withdrawn from the open-label study on study day 51 as a result of the second occurrence of rash.

#34015- Patient 034015, a 6-year-old girl of mixed race (black and white) with ADHD, started treatment with modafinil on 23 December 2005. Study drug was started at 85 mg/day on day 1 and was titrated to 170 mg/day on day 3 and to 255 mg/day on day 8. Her medical history included bronchitis, seasonal allergies, tonsillectomy and adenoidectomy. Cetirizine hydrochloride was taken for seasonal allergies prior to the study and continued concomitantly. This patient had not taken any prior medication for ADHD. On day 2, the patient experienced a nonserious, mild infection (verbatim: upper respiratory infection) and was given diphenhydramine hydrochloride and bromfed. The upper respiratory infection resolved on day 6. On day 10, the patient developed a severe rash (verbatim: rash on arms and legs - small red lesions on arms and confluent large area on inner thighs), which was a nonserious adverse event. She was treated with diphenhydramine hydrochloride and hydrocortisone cream, and study drug was

discontinued on day 13, and she was withdrawn from the study. The rash resolved 3 days later with no residual effect, and no additional adverse events were reported. The investigator considered the upper respiratory infection to be not related to study drug and the rash to be probably related to study drug.

Comment: Although the rash could be part of a viral infection that initially manifested on day 2 of the trial, it could also be a drug reaction, independent of the initial respiratory infection.

#19010- This 11-year-old white boy with ADHD began treatment with 300 mg/day of modafinil on 27 April 2002. He took study drug a total of 21 days during the double-blind treatment period, and his last dose was taken on 17 May 2002. Other than for ADHD, his medical history was not significant. At study entry, this child was not taking any other medication. Nine days before beginning treatment with study drug, an adverse event of mild headache (COSTART: headache) was reported. The headache resolved with no residual effect the same day. On study day 17, an adverse event of moderate rash was reported. The rash was considered resolved with no residual effect 12 days later. The patient withdrew consent and withdrew from the study on study day 21 (four days after the onset of rash). The investigator considered both the rash and the headache to be probably related to study medication.

Although the reason for discontinuation is "withdrew consent", this occurred right after onset of the skin rash, therefore, withdrawal was likely related to this adverse event.

3.c- Listing of cases with skin reactions that do not appear to be hypersensitivity reactions

48017 - Plantar warts, no rash
49327 - Flushed face, no rash
58006 - Ringworm - fungal dermatitis
2007 - Blotches on tongue and gastroenteritis
3016 - Varicella
31007 - Dry mouth, no rash
34004 - Dry mouth, no rash
49017 - "Worsened allergies" (no description of what kind of allergies)
034007 - Eczema and elevated transaminases. Patient had a history of eczema and continued having eczema throughout the trial.

3.d. Cases in which there were skin reactions but patient discontinued the trial because of other reasons

48361 - Possible allergic reaction but also a dystonic reaction, more likely to have been the cause of discontinuation
405 - Rash but the reason for discontinuation was suicidal ideation
31149 - Pruritus, no rash, and had other symptoms that led to discontinuation
42309 - Rash but the cause of discontinuation was a duodena ulcer
57006 - Patient was treated with Benadryl on day 23 for an unknown reason (no mention of rash); the drug was not discontinued at that time.

Appendix 4. Modafinil skin rashes - Discontinuations in Adults

Study Number: C1538a/413/DP/US

Patient ID# 028356, **Treatment:** PROVIGIL (200 mg)

Adverse Event(s) Leading to Withdrawal: rash generalized

This 24-year-old white woman with depression began double-blind treatment with PROVIGIL (200 mg) on 6 June 2003. She had a history of cat dander allergy. She received concomitant multivitamins, spirulina, and other combinations of nutrients (supplement), and paroxetine hydrochloride (for depression). Beginning on day 6, she had a moderate generalized rash (entire body) that led to withdrawal from the study on day 7. Her last dose of study drug was on day 6. She received loratadine hydrochloride for the rash. The rash, considered to possibly be related to treatment with the study drug, resolved with no residual effect on day 13.

Study MOD-028/Narcolepsy / Hypersomnia

Patient ID# D16 ~~-----~~ **Treatment:** Modafinil, 200 mg total daily dose, OL

Adverse experience(s): 74 year old male experienced two episodes of itching and eruption while receiving modafinil. None of the events were serious. The first episodes of itching and eruption resolved but the outcome of the second episode is unknown. Study drug was discontinued due to the second episodes.

b(6)

Study Open/2-2/ Out-patients with "neurosis"

Patient ID# ~~-----~~ I 3/ ~~-----~~, **Treatment:** Modafinil, 100 mg twice daily, open

Start date : Unknown **End date:** Unknown **Duration:** 4 days

Adverse experience(s): 50 year old female, Urticaria began on Day 2. It was considered to be of an unknown intensity and lasted for an unknown period of time. This event was not considered serious and was ongoing at the time of reporting. Study drug was discontinued because of this event.

b(6)

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Appendix 5.a. Armodafinil skin rashes. Discontinuations (all adult patients)

Patient 3183008, a 46-year-old white man with narcolepsy and history of cardiovascular disease, received 150 mg of **armodafinil** per day in study C10953/3020/NA/MN and began treatment with open-label armodafinil on 10 October 2004, which was increased up to 250 mg/day. Prior medications that were continued during the study were atorvastatin and lansoprazole. Additional concomitant medications that were administered during the study included dexamethasone, morphine, intravenous sodium chloride, OXYCOCET®, propofol, ketorolac tromethamine, and ondansetron hydrochloride related to a surgical procedure (hemorrhoidectomy, Day 154). Armodafinil dosage was decreased to 200 mg on day 28 due to an adverse event of nausea and mild numbness in his limbs. Physical examination on day 74 revealed a skin rash on the patient's arms and legs, which was reported as a mild adverse event of unknown start date; the patient received no treatment for the skin rash. For the remainder of the study, armodafinil dosage varied between 100 mg and 200 mg/day. Study drug was discontinued on day 448 as a result of the ongoing skin rash on the patient's arms and legs.

Comment: Although it appear to be extensive (arms and legs) there is no description of the rash. It is unclear why if it was discovered on day 74 and did not require treatment, it led to drug discontinuation on day 448.

Patient 0821864, a 50-year-old white woman with OSAHS, began treatment with **armodafinil** on 17 June 2004 in study C10953/3025/AP/MN (dose: 150 mg/day). Medical history included environmental allergies. Prior and concomitant medications continued while in the study, included ibuprofen, multivitamins, levothyroxine sodium, atorvastatin, and etodolac (started day 16/stopped day 20). On day 28, the patient developed a nonserious, papular rash that was moderate in intensity. Study medication was discontinued on day 55 due to the rash, and the patient was withdrawn from the study. The adverse event was continuing at the time of study withdrawal; the rash was treated with hydrocortisone and azithromycin (both started day 76). Additional adverse events included intermittent hand and arm paresthesia.

Comment: Again, there are no details about the skin rash, but the event is described as being of "moderate" intensity on Day 28, that led to discontinuation on Day 55.

Patient 2461960, a 53-year-old Asian man with OSAHS, began treatment with **armodafinil** on 25 July 2004 (study C10953/3025/AP/MN) (dose: 150 mg/day). Medical history included environmental allergies (sinus suggestion). Prior and concomitant medication taken by the patient included terbinafine. An ECG performed on day 27 showed a non-specific intraventricular conduction defect (IVCD); however, this abnormality was not considered an adverse event. On day 28, the patient developed a rash of moderate in intensity. Study drug was discontinued on day 30 due to the adverse event, and the rash was treated with diphenhydramine hydrochloride and hydroxyzine. The rash resolved with no residual effect on day 41, and the patient was withdrawn from the study 5 days later (day 46).

Comment: Patient developed a skin rash of moderate intensity on day 28, leading to drug discontinuation on day 30, and treatment with diphenhydramine and hydroxyzine. Again, no description of the rash was provided.

Patient 1549062, a 26-year-old black man with chronic SWSD, began treatment with

armodafinil on 23 July 2004 (study: C10953/3025/AP/MN) (dose: 150 mg/day). Significant medical history included penicillin allergy and hemorrhoids. No prior medications were reported. On day 26, the patient developed a non-serious neck and upper chest **rash** (MedDRA: rash) that was moderate in intensity. Study drug was discontinued that same day (day 26), and the rash was treated with diphenhydramine hydrochloride and hydrocortisone. The patient was withdrawn from the study on day 27, and the rash, which the investigator considered to be probably related to study drug, resolved with no residual effect on day 29. No additional adverse events or medications were reported.

Patient 8486012, a 20-year-old white woman with narcolepsy, began treatment with **armodafinil** on 28 October 2004 (study C10953/3020/NA/MN) (dose: 250 mg/day). Significant medical history included allergies to nicotine, antibiotic, novocaine, and honey. No prior medications were reported. On day 10, the patient experienced sleep disturbance and moderate behavior disorder and the next day (day 11), she developed nonserious, moderate **urticaria**. The urticaria was treated with chloropyramine (day 11 and day 12) and loratadine (day 13 through day 22). Study drug was discontinued on day 18 due to the sleep disorder, abnormal behavior, and urticaria; all 3 of these adverse events resolved on day 36, and the patient was withdrawn from the study that same day. The urticaria resolved with no residual effects; however, residual effects of the sleep disorder and abnormal behavior persisted at the time of withdrawal. The investigator considered all 3 of these adverse events to be probably related to study drug. No additional adverse events or medications were reported.

Patient 0821838, a 46-year-old black woman with OSAHS and a history of environmental allergies, began treatment with placebo on 30 May 2004 (study C10953/3025/AP/MN). Prior and concomitant medications taken by the patient, all of which she continued while in the study, included ascorbic acid, ergocalciferol, aspirin, tocopherol, hormones and related agents, vitamins, esomeprazole (started day 14), butenafine (started day 12), clarithromycin (started day 12 and stopped day 2), and amoxicillin (started day 12 and stopped day 2). On day 68, the patient developed a mild, nonserious, **macular, hyperpigmented lesion on her left cheek** (MedDRA: rash macular). Study drug was discontinued 5 days later (day 73) due to the event, and the patient was withdrawn from the study. The macular rash resolved with no residual effect on day 75. Additional concomitant medications included fluvastatin sodium and cefadroxil.

Patient 0841739, a 35-year-old white woman with OSAHS, began treatment with placebo on 15 August 2004 (study C10953/3021/AP/MN). Prior and concomitant medications taken by the patient, all of which she continued while in the study, included naproxen sodium, ibuprofen, multivitamins. She developed mild **tinnitus** (MedDRA: tinnitus) on day 1 subsequent study drug administration. On day 3, she developed moderate **hives** (MedDRA: urticaria) that were treated with loratadine (on days 3 and 4); study drug was discontinued due to both adverse events. The hives resolved on day 4, and the tinnitus resolved day 5; the patient was withdrawn from the study on day 6. Both of these adverse events resolved with no residual additional adverse events.

Patient 2669161, a 54-year-old black woman with chronic SWSD, began treatment with placebo on 1 October 2004 (study C10953/3022/CM/MN). Significant medical history included hypertension, mild osteoarthritis, and mild rheumatoid arthritis. No concomitant medications were reported; however, the patient received loratadine for hives prior to entering the study (taken on day 58). On day 2, the patient developed a nonserious, mild rash/urticaria on her lower extremities (MedDRA: urticaria). Study drug was discontinued on day 6 due to the urticaria, which the investigator considered to be possibly related to study drug, and the urticaria resolved with no residual effect that same day. The patient was withdrawn from the study on day 29. No additional adverse events were reported.

Appendix 5.b. Patients who discontinued for reasons other than a skin rash, but also had a skin rash.

Patient 2161856, a 46-year-old white woman with OSHA, received 150 mg of **armodafinil** per day in study C10953/3025/AP/MN and began treatment with open-label armodafinil on 27 August 2004.

Comment: This case appears to be an intertriginous rash that did not lead to discontinuation.

Patient 3183004, a 24-year-old white woman with narcolepsy, began treatment with **open-label armodafinil** on 14 September 2004. She developed intermittent facial rash described as dermatitis, and increased GGT.

Comment: It is unclear whether the facial rash was in fact dermatitis and the dates of the event are also unclear. The value and the date for the increase of GGT are not provided either. In any case, neither the facial rash nor the abnormal GGT appear to have been clinically important and did not lead to discontinuation.

Patient 036001, a 50-year-old white woman with OSAH began treatment with **armodafinil** on 18 January 2006 (study C10953/3046/ES/US). Her medical history included allergy to iodine and chronic nasal congestion. Prior medications that were continued during the study included levothyroxine, venlafaxine, ibuprofen, thomapyrin N and budesonide. Study drug was titrated to 150 mg on day 4 and the patient continued receiving this dose. **On day 47, a mild adverse event of rash** was reported; the patient received treatment with fluocinonide and cetirizine for the rash. A very mild erythematous rash (suboccipital, neck/ shoulders) was noted at the physical examination on day 57. **On day 57**, the last day of the short-term treatment period, moderate adverse events of increased blood alkaline phosphatase (Alk phosp) and **elevated liver enzymes** (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma-glutamyl transpeptidase [GGT]) were reported. Treatment with **armodafinil was discontinued on day 59 due to the increased alkaline phosphatase and elevated liver enzymes**. Abdominal tenderness was reported on day 78. At that time, ALT, AST, and Alk phosp values had returned to within normal limits. The only other serum chemistry abnormalities were a high glucose value (131 mg/dL on day 62, normal range 70 to 115 mg/dL) and high calcium values (10.7 mg/dL on days 69 and 78 and 10.9 mg/dL on day 85, normal range 8.3 to 10.6 mg/dL). No hematology, vital signs, or ECG abnormalities were reported for the patient during the study. The following adverse events were also reported: dizziness (days 4 to 57), dry mouth (days 8 to 57), weight decreased (day 15, not resolved at study end), decreased appetite (days 15 to 57), arthralgia (day 60, not resolved at study end). A bilateral shoulder rash that was almost resolved (faint erythema) was noted at the final physical examination on day 78 and was not resolved at the time of the patient's withdrawal from the study on day 105. Alkaline phosphatase, ALT, AST, GGT, and total bilirubin values for patient 036001 are provided below.

Study day	Alkaline phosphatase (normal, 35-123 U/L)	ALT (normal, 6-34 U/L)	AST (normal, 9-34 U/L)	GGT (normal, 4-49 U/L)	Total bilirubin (normal, 0.2-1.2 mg/dL)
-8	63	18	21	17	0.3
57	215	191	103	426	0.5
62	188	89	39	355	0.3
69	136	32	25	241	0.3
78	99	21	26	152	0.4
85	86	19	25	103	0.3
98	79	23	24	60	0.2
105	76	19	24	49	0.5

Appendix 6. All adverse events pertaining to the MedDRA SOC Skin and Subcutaneous (S/C) Tissue disorders and Immune System disorders in armodafinil studies

SOC MedDRA PT	Placebo-controlled studies		All studies
	Armodafinil 150 & 250 mg/d N= 645 n (%)	Placebo N= 445 n (%)	Armodafinil 150 & 250 mg/day N= 1516 n (%)
Immune system disorders	5 (<1)	2 (<1)	44 (3)
Seasonal allergy	4	1	26 (2)
Allergy to arthropod bite	1	-	1
Allergy to arthropod sting	-	-	1
Hypersensitivity	-	1	15
Food allergy	-	-	1
Skin and S/C Tissue disorders	41 (6)	18 (4)	171 (11)
Rash	13 (2)	1	49 (3)
Dermatitis contact	7 (1)	2	20 (1)
Hyperhidrosis	4	1	21 (1)
Pruritus	3	1	13
Pruritus generalized	-	-	3
Urticaria	3	4	9
Rash macular	2	1	2
Acne	1	-	7
Angioedema	1	-	1
Dermal cyst	1	1	5
Dermatitis	1	-	2
Dermatitis allergic	-	-	4
Dry skin	1	-	7
Eczema	1	-	2
Erythema	1	-	2
Night sweats	1	-	6
Heat rash	-	-	4
Rash papular	1	-	2
Rash vesicular	-	-	2
Rash erythematous	-	-	1
Skin irritation	1	1	3
Skin ulcer	1	-	3
Swelling face	1	-	2
Stasis dermatitis	-	-	2
Urticaria contact	1	-	1
Alopecia/Alopecia areata	-	1	2
Ecchymosis/bruising	-	1	1
Ephelides	-	1	-
Psoriasis	-	1	4
Rash pruritic	-	1	-
Rosacea	-	-	1
Skin odor abnormal	-	1	-

Source: Safety Update, April 16, 2007, Complete Response, Summary 4.1.1 & 4.1.3. In addition to the listed events, there were one case each of: cold sweat, ingrown hair, ingrown nail, intertrigo, keloid scar, pain of skin, palmar erythema, photosensitivity reaction, pigmentation disorder, precancerous skin lesion, scar, skin lesion and skin warm, in the "All Studies" dataset. Patients are counted only once in each preferred term category and only once in each system organ class category.

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6/15/2007 04:48:25 PM
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Review of Clinical Data

NDA#: NDA 20-717 (modafinil) and NDA 21-875 (armodafinil)
Sponsor: Cephalon
Subject: Serious skin and hypersensitivity reactions
Material: December 19, 2006 submission related to severe cutaneous adverse reactions with modafinil; February 7, 13 & 23, and March 16 & 21, 2007 responses to FDA informational requests; February 23, 2006 label amendment for NDA 21-875. Previous reviews by DNP and DPP Medical Officers, OSE/DDRE and Dermatology consultants.
Date: March 22, 2007
Reviewer: Lourdes Villalba, M.D., Medical Officer, Safety Team, DNP/DPP.
Team Leader: Alice Hughes, M.D., Safety Team, DNP/DPP

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Executive Summary

Provigil™ (modafinil) is currently approved in adults as a wakefulness-promoting agent. The sponsor of Nuvigil™ (armodafinil), the R-enantiomer of modafinil, is seeking approval to market Nuvigil for similar indications. Concerns regarding serious hypersensitivity reactions associated with these two drugs were raised in 2005, during the FDA review of an efficacy supplement of modafinil for children and adolescents with attention deficit hyperactivity disorder (ADHD).

This review addresses several questions raised by the FDA in a meeting with Cephalon held on October 26, 2006. The data reviewed indicates a relationship between the use of modafinil and the onset of serious hypersensitivity reactions, including erythema multiforme major (EMM), Stevens-Johnson syndrome (SJS), toxic epidermic necrolysis (TEN) and multi-organ hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS).

- Clinical trial data

The review of the modafinil clinical trial database suggests a higher risk of serious skin and multi-organ hypersensitivity reactions in the pediatric population as compared to adults.

- Pediatric clinical trials (n=1622 exposed to modafinil in controlled and open label studies)

One case of SJS (or atypical EMM), in a 7 year-old male on Day 15 of modafinil treatment was observed in the pediatric trials. The estimated crude rate of SJS in this

database is 1/1622= 0.06 %. The background rate of SJS is 1-2 cases per million person years of exposure and it is associated with 15% mortality.¹ (Even if this is a case of atypical EMM, as sustained by Cephalon, the diagnosis is not completely benign.)

In addition to this case, seven subjects, ages 6 to 12 years, presented with a cutaneous reaction that required discontinuation, sometimes with hospitalization – rash alone or accompanied by fever (n= 4); elevated transaminases (n=1) or leukopenia (n=2) - suggesting early SJS or multi-organ hypersensitivity reactions. No adequate clinical or laboratory follow up information was available in most of these cases. The crude rate of skin reactions requiring discontinuation, including the case of SJS, was 8/1622 = 0.5%. No such cases occurred in children receiving placebo.

- Adult clinical trials (n=4178 in controlled and open label studies)

No serious skin of multi-organ hypersensitivity reactions were observed in adult subjects in modafinil trials.

- Postmarketing database (1.8 million unique patients from 1999 through August 2006 in the US; 2.6 million unique patients from 1994 through August 2006 worldwide)

No cases of Severe Cutaneous Adverse Reactions (SCARs) were found in the EuroSCAR, the RegiSCAR, and the German SCAR registry. These studies cover approximately 58,000 subjects exposed to modafinil, of whom approximately 3% were <19 years of age. The lack of cases of SCARs in the European postmarketing databases is not reassuring as the estimated exposure to modafinil in these databases is too small to address uncommon events such as SJS and TEN, particularly for the pediatric population (approximately 1700 subjects).

Six SCARs and eight potential multi-organ hypersensitivity reactions were identified in the modafinil postmarketing database as of February 2007. All cases were domestic. Most of the postmarketing cases were confounded by concomitant medications (lamotrigine, n=3; oxcarbamazepine, n=1; celecoxib, n=1), or comorbidities (systemic lupus erythematosus, n=2; HIV+, n= 1) and contained limited/insufficient information. However, there was a temporal relationship with modafinil use for all of the cases, with two cases of positive re-challenge, which is supportive of a causal association (see Appendix 1).

The estimated use of modafinil in the US from January 2002 through Dec 2006 was _____PYRs or _____ unique patients, of whom _____ were <19 years of age.²

b(4)

¹ Rzany, Mockenhaupt, Baur, Schroder, Stocker, Mueller, Hollander, Bruppacher & Schopf. Epidemiology of rare serious cutaneous adverse reactions. Results of the population based registry for erythema exsudativum multiforme with mucosal involvement (EMMM), Stevens-Johnson-syndrome (SJS) and toxic epidermal necrolysis (TEN) in Germany. J. Clin. Epidemiol., 1996.

² Verispan Vector One™ data and Total Patient Tracker™, 2002-2006, provided by Carol Pamer, Drug Use Specialist, OSE/DSRCS. Extracted 01/30/07.

The reporting rate of SJS/TEN in AERS was estimated by Dr. Lois La Grenade, a dermatologist and epidemiologist in OSE/DDRE, using rigorous case definition criteria. In this conservative analysis that included only 4 cases (including a 17 year old subject), the estimated reporting rate of SJS/TEN through December 2006 was **5.7 cases per million PYRs for patients of all ages**, which is above the background rate of 1-2 cases per million PYRs reported in the literature. Given the known phenomenon of under reporting, this finding is of concern. For comparison, the reporting rate of SJS/TEN in AERS with celecoxib, a COX-2 selective non-steroidal anti-inflammatory drug (NSAID) has been estimated to be 6 cases per million PYRs, and for valdecoxib, another COX-2 selective NSAID, 49 cases per million PYRs.³ Of note, celecoxib carries a WARNING for severe skin reactions, including fatal SJS and TEN. Valdecoxib was withdrawn from the market in 2005 in part because of these adverse reactions.

If we use a cut-off age of 16 years for the analysis of pediatric cases, there are no cases of SJS/TEN in this age group in the postmarketing database (although there was a case of DRESS in a 15 year old subject). The estimated exposure to modafinil in the pediatric population is relatively small _____ of the total exposure). Therefore the analysis of postmarketing events does not rule out the possibility of a higher risk of serious cutaneous reactions in the pediatric population that has been raised in the clinical trials.

It is unknown how the risk of these serious adverse reactions with armodafinil compares to the rate observed with modafinil. There were no cases of severe cutaneous or systemic hypersensitivity reactions in the armodafinil clinical studies. There was a case of angioedema and one anaphylactoid reaction in the armodafinil database. The crude rate of angioedema in the armodafinil database is $1/1595 = 0.06\%$, a rate close to that of the ACE inhibitors (2-10 per 10,000 new users).⁴

This reviewer recommends:

- 1) Prominent location of the information related to serious skin and multi-organ hypersensitivity reactions with modafinil in the WARNINGS section of the Provigil and Nuvigil labels.
- 2) Collection of additional information to better address the benefit/risk ratio of modafinil before it is approved for use in the pediatric population. We concur with the need of a _____ as previously recommended by the DPP.
- 3) Prominent information that Provigil (and Nuvigil) is not approved for use in children and adolescents. Because Provigil is already being used and Nuvigil is likely to be used off-label in the pediatric population, and because the clinical trials suggest a higher risk of serious skin and hypersensitivity reactions in children. _____

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b(4)b(5)

³ La Grenade et al. Comparison of SJS and TEN in association with selective COX-2 inhibitors. Drug Safety, 2005.

⁴ Roujeau. Clinical heterogeneity of drug hypersensitivity. Toxicology, 2005.

b(4)

b(5)

- 4) The sponsor needs to make an effort to improve the follow up of cases with serious skin and hypersensitivity reactions in ongoing and future clinical trials of modafinil and armodafinil, as well as in postmarketing reporting. Any ongoing or further studies with these drugs need to incorporate into the protocol an adequate follow up of these cases, including dermatologic evaluation, laboratories (CBC, transaminases), photographs, biopsy results, and if applicable, final diagnosis, treatment received, and information regarding clinical outcome.
- 5) A risk minimization plan (RMP). In addition to labeling changes, a RMP could include quarterly reports to the NDA (separate from the regular Periodic Reports or PSURs) of new cases of serious skin/hypersensitivity reactions, a Dear Healthcare Professional letter, educational materials for physicians and patients, etc.
- 6) Angioedema and anaphylactoid reactions should be included in the WARNINGS section of the label.

1. Background

1.1 Regulatory history

Provigil™ (modafinil, NDA 20-717) was approved on December 24, 1998, for the treatment of adults with excessive daytime sleepiness associated with narcolepsy. The indication was later extended to the treatment of obstructive sleep apnea/ hypopnea syndrome (OSAHS) and shift work sleep disorder (SWSD).

- **NDA 20-717s019 (Sparlon™, modafinil, for pediatric ADHD)**
 - On December 20, 2004, Cephalon submitted an efficacy supplement to NDA 20-717 for the treatment of children and adolescents with ADHD.
 - On October 20, 2005, the FDA issued an Approvable letter. The studies supported the short-term efficacy of modafinil for ADHD in the pediatric population. Safety concerns (one of them being three cases of clinically important rash, including one presumptive case of Stevens Johnson Syndrome (SJS) in a 7 year-old boy) warranted additional assessment before the drug could be approved for ADHD.
 - On February 17, 2006, Cephalon submitted a Complete Response to DPP's October 20, 2005 AE letter.
 - On August 9, 2006, the DPP issued a Not Approvable letter to NDA 20-717s019. The letter suggested the need ~~_____~~

b(4)

- **NDA 21-875 (Nuvigil™ for adult narcolepsy, OSAHS, SWSD)**

- On March 31, 2005, Cephalon submitted NDA 21-875 for approval of armodafinil, (the R-enantiomer of modafinil), for the same indications as Provigil.
- On April 28, 2006, the DNP issued an Approvable letter for this application. The studies supported the efficacy of Nuvigil for the proposed indications, but safety concerns precluded its approval. Among other requests, the DNP asked for additional data related to serious rash and multi-organ hypersensitivity reactions associated with modafinil dating back to the ADHD NDA.
- On June 30, 2006, Cephalon submitted a Complete Response to the April 28, 2006 AE letter.
- On February 23, 2006, Cephalon submitted an amendment to the proposed label.

b(4)

1.2 Rationale for FDA's concerns with modafinil/armodafinil hypersensitivity reactions.

- Three cases of clinically important rash, including one case of SJS in a 7 year-old boy (subject # 062338) and one multi-organ hypersensitivity reaction in a 9 year old boy (subject # 056180) were observed during the pediatric ADHD clinical studies (Dr. Glenn Mannheim, HFD-130 medical reviewer) The observation of one case of SJS in a small database raised concerns, as SJS is an uncommon adverse reaction with a reported background rate of 1-2 cases per million patients per year, with a 5-15% mortality rate.¹ The sponsor argued that this case was not definitive SJS. Dr. Markham Luke, a consultant from the Division of Dermatologic and Dental Drug Products (DDDP), concluded that modafinil could not be ruled out as a possible cause of this serious skin reaction (October 12, 2005).
- A review of the FDA Adverse Event Reporting System (AERS) by the Office of Surveillance of Epidemiology, Division of Drug Risk Evaluation (Charlene Flowers, RPh., Safety Evaluator, OSE/DDRE, October 19, 2005) identified four cases of serious skin reactions with modafinil through August, 2005 (Cases 1-4, see Appendix 1).
- On February 27, 2006, Dr. Joseph Porres, also a consultant from the DDDDP, conducted a comprehensive review of available safety with modafinil, to identify cases of SJS and erythema multiforme (EM). The data came from 933 patients in the original ADHD efficacy supplement, 533 patients from an ongoing Phase 3 open

label study, and post-marketing spontaneous reports submitted by the sponsor (cut-off August 2005). He identified a total of six cases of EM and/or SJS ([EM/SJS] (two pediatric cases from the ADHD studies and four adult cases from spontaneous reports); fifteen cases that might represent cases of EM/SJS but the information provided was insufficient for a definitive determination; and sixteen cases resembling a possible prodromal/incomplete presentation of EM/SJS. These adverse reactions ranged in severity and a few required hospitalization but all resolved upon treatment cessation and none lead to death or permanent disability. One of the two pediatric cases of EM/SJS was later determined to be a morbilliform rash.

- Dr. Judy Racoosin (DNP/DPP Safety Team, April 6, 2006) estimated the reporting risk of EM/SJS in patients receiving modafinil, using AERS reports of EM/SJS from January 2002 through December 2005 as the numerator (n=5) and Verispan™ Total Patient Tracker, from January 2002 through November 2005 as the denominator (Appendix 1, cases 1-5). The overall reporting risk of EM/SJS was cases per million patients. The analysis was further broken down by age. If one considers the one case in the 7 year-old subject that was submitted to AERS (which came from one of the clinical trials) as a postmarketing case, the reporting risk in 0-12 year olds for the period 2002-2005 was cases per 1 million patients. However, excluding this case, there were no other spontaneous reports of severe skin rash in a child or adolescent reported to AERS, despite off-label use of modafinil in approximately 36,000 pediatric patients.
- A follow-up OSE/DDRE review of serious cutaneous adverse reactions in AERS (Oluchi Elekwachi, Pharm. D., MPH, August 1, 2006) found one new case of SJS/TEN (ISR# 467929) and one case of hypersensitivity-associated myocarditis with eosinophilia (ISR# 5013599). Both these cases were fatal (See Appendix 1). The contribution of modafinil to these deaths was unclear.
- On March 23, 2006, the Division of Psychiatric Products convened a Psychiatric Drug Advisory Committee (PDAC) to discuss the safety and efficacy of modafinil in the treatment of ADHD. PDAC recommended not approval in a 12:1 vote based on the single suspicious case report of SJS. In order to adequately characterize the risk of SJS in association with modafinil treatment, the PDAC recommended that a _____ _____ _____ would be sufficient evidence of safety to allow them to recommend approval. _____
- Additional information and photographs related to case # 062338 were submitted to the Agency in April 2006. Upon review of this information, Drs. Michael Bigby (a dermatologist) and Wayne Goodman (both members of the PDAC) concluded that case 062338 (also referred to as 311/062338 and VVP062009) was a definite case of SJS. Dr. Luke stated again that SJS can not be ruled out for this case.

b(4)

b(4)

- On June 30, 2006, Cephalon submitted a Complete Response to the April 28, 2006 AE letter for Nuvigil. As part of this response, Cephalon reviewed their clinical trial database for possible cases of serious rash and multi-organ hypersensitivity reactions with modafinil. The database includes controlled and uncontrolled modafinil studies, involving 4178 adults and 1622 children and adolescents. The June 30, 2006 complete response was reviewed by Dr. Wilson Bryan, Team Leader (in a review dated December 21, 2006). **A summary of Dr. Bryan's findings are as follows:**

- Serious Rash in the June 30, 2006 submission

The search for cases of serious rash included cases that fulfilled the regulatory definition of serious, cases of skin adverse events that led to withdrawal from a study, and any case of withdrawal from a study due to an adverse event that contained any reference to skin adverse event (even if the skin adverse event was not the nominal reason for study withdrawal). One hundred and nine subjects were evaluated for a potentially serious rash in the modafinil clinical trial database.

Of the 109 subjects, all but five were not considered further for the following reasons:

- a) They had a probable benign drug eruption, a rash that was not likely to be a drug eruption, a rash that was likely a component of an infectious syndrome, or insufficient narrative information to assess the rash (n=18)
- b) They had a clinical course, outcome or associated findings that indicated that the rash was not "serious (clinically meaningful)." (n=29)
- c) There was no reasonable temporal relationship between the event of rash and withdrawal from a study (n=50)
- d) They had a rash with no mucous membranes involvement that did not require discontinuation of study medication for management of the rash (n=9)

The five cases considered by Dr. Bryan as potentially serious skin reactions are as follows:

- Subject # 062338, from study 311, (7 y.o. M) had SJS (or as per the sponsor, atypical EMM). He was titrated to modafinil 425 mg/day by Study Day 14. On Day 16, he had fever of 101.9 °F, sore throat and a rash described as red bumps. On day 17, he had a single dose of amoxicillin. On Day 18, the modafinil was stopped. Over the next 4 days the skin reaction progressed from multiple pruritic areas on his arms/stomach (day 19) to involve his face and mucosa (urethral meatus/swollen crusty lips). After a period of extensive skin peeling which included his palms and soles, his skin reaction resolved with no new lesions noted. He was rechallenged with modafinil and the pruritis returned. He was withdrawn from the study on Day 44, after the positive rechallenge.
- Subject # 315 (11 y.o. F), on day 4 had fever (101°F), abdominal pain and diarrhea that lasted 9 days. On day 14 she was seen in the ER with generalized rash (described as pruritic urticaria on the face and chest) and was hospitalized with a

provisional diagnosis of SJS. Modafinil was discontinued on day 15. A **dermatologist determined that this was a “moderate morbiliform rash.”** The rash resolved within a week.

- Subject # 18004 (8 y.o. M) had a moderate rash on the cheeks and severe blisters on his lips. Modafinil was discontinued and the rash resolved. The narrative does not include sufficient information for a more definitive assessment.
- Subject #056180 (9 y.o. M) The patient had a history of sulfa allergy and ADHD who began open label treatment with modafinil on Feb 25, 2004. Modafinil was titrated up to 340 mg/day by Day 10. On Day 13 he developed fever, urticaria, hives, swollen eyes and vomiting. Modafinil was discontinued and fever resolved. **The urticaria and eye swelling resolved on Day 23. The rash was “petechia-like not “maculopapulous” ” on cheeks, limbs and abdomen.** On Day 14, ALT level was 517 (normal range 5-30 U/L) and AST level was 409 U/L (normal range 0-40 U/L). ALT and AST levels were back to normal by Days 23 and 35, respectively. This case of multi-organ hypersensitivity is relatively mild, but is not clearly confounded.
- Subject # 18001 (6 y.o. M) had a severe macular rash, fever and vomiting. The drug was discontinued and the rash resolved in 15 days. This case could have been early or mild SJS but limited information is available.

Comment: All five cases came from the pediatric clinical trials. After discussion of these cases at the PDAC, only subject # 062338 is considered to have had SJS and Subject #056180, was considered to have a multi-organ hypersensitivity reaction. For the other three, limited information is available for a definitive diagnosis.

No additional cases of serious rash were identified from the postmarketing database.

- Multi-organ hypersensitivity in the June 30 submission

Multi-organ hypersensitivity was defined by the sponsor as the presence of internal organ involvement (e.g., hepatitis, nephritis, carditis) combined with at least two of the following: fever, rash, lymphadenopathy.

Thirteen potential cases matched these search criteria in the pre-marketing database, but a single case was identified as multi-organ hypersensitivity. It was subject #056180, mentioned above, from the pediatric clinical trials. No cases were found in adult trials.

Fifteen potential cases matched this search criteria the postmarketing database through April 30, 2006. Of these, **seven were identified by Dr. Bryan as potential multi-organ hypersensitivity**, including one case of DRESS in a 15 year old male, as follows:

- ISR/#5060040 - A 15 year old male initiated Provigil on 4/13/03 with incrementing doses up to 400 mg daily for the treatment of ADHD. **Five weeks later**, he presented with a generalized body rash with fever, followed by fatigue, myalgia, vomiting, rhinorrhea and dry cough. Fever was treated with ibuprofen. Subsequently, the patient was hospitalized and all medications including Luvox, Zyprexa, and Abilify that were prescribed since 2005 and Provigil were discontinued. On admission, he had a maculopapular rash with no mucosal involvement but with soft palate petechiae and facial edema. Admission blood laboratory values revealed 37% eosinophils, **25,000 WBC's, and BUN/ creatinine levels** suggesting a pre-renal state. A dermatologist diagnosed it as a **drug reaction with eosinophilia and systemic symptoms (DRESS)**, subsequent to a skin biopsy (site unspecified) which showed eosinophilia and unspecified findings consistent with drug hypersensitivity syndrome. Within 24 hours of admission, the patient showed signs of coagulopathy. Palmar petechiae were observed, and the patient was unable to eat; his face, hands, and feet were markedly edematous, and he continued to experience intermittent pyrexia. Meanwhile, blood titers were negative for IgM, measles, and Rubella. **All viral and bacteria cultures were negative. In a short time, the patient's vital signs** became unstable with bradycardia and hypotension. A chest x-ray revealed bilateral, fluffy alveolar opacities and alveolar edema. The patient was transferred to the intensive care unit where he was placed on mechanical ventilation. The patient was supported with dopamine for blood pressure support and steroids and intravenous immunoglobulin therapy. He developed pancreatitis and hepatitis. Labs (amylase 542 (reference range=40 -220), lipase 788 (reference range=7 - 60), AST 240 (reference range=2-40), and ALT 186 (reference range=3-30). The patient remained hemodynamically stable and the patient was extubated on 6/2/06. Coagulopathy, eosinophilia and leukocytosis had resolved. All viral and bacteria cultures remained negative. Desquamation of the rash continued but was showing signs of recovery.

Comment: This is a dramatic case with multi-organ involvement. The case is confounded by concomitant use of other drugs and the use of ibuprofen to treat the fever (unclear how many doses). However, modafinil was the most recently added drug and the rash/fever/fatigue/myalgias preceded the use of ibuprofen.

Narratives of the other cases are presented in Appendix 1.

The available information was generally insufficient and almost all of the post-marketing cases were confounded. However, the controlled trial case (subject #056180) was strongly suggestive of multi-organ hypersensitivity due to modafinil.

b(5)

- On further review of the June 30, 2006 submission, I found some additional cases of interest (**not described in Dr. Bryan's review**):
 - Subject # 020001 (Study C1538/3044/AD/US) 12 y.o. girl with ADHD. She was not taking any medication within 30 days before beginning treatment with

modafinil. On Day 13, she developed moderate urticaria (hives) and was treated with methylprednisolone, oral corticosteroids and diphenhydramine at a physician's office. Although "non-serious", this event prompted discontinuation from the trial.

- Subject # 014724, an 11-year-old girl with narcolepsy, began treatment with 100 mg/day of PROVIGIL in an open-label extension study on 11 October 2005; she had been treated with 100 mg/day of PROVIGIL in the previous study. She had no significant medical history and was taking no concomitant medications at enrollment. On day 2, she had moderate adverse events of arthralgia and joint swelling in limbs bilaterally, both of which the investigator considered possibly related to treatment with study drug. Modafinil was discontinued on Day 2. The patient was given ibuprofen and the events were considered resolved without residual effect on day 6. She also developed a mild rash (verbatim: rash on the thighs) on day 5 that was considered possibly related to treatment with study drug. The rash resolved without residual effect the following day.

Comment: The reason for discontinuation in this patient was coded as "arthrosis". However, joint swelling (Day 2) and rash (Day 5) are not inconsistent with a systemic hypersensitivity reaction, although the rash appeared after the drug was discontinued. It is unclear for how long had she been taking modafinil in the base study. Follow up is not available.

-Subject # US010763, 22 y.o. female, initiated modafinil 200 mg/d on 2/27/03. After the second dose she experienced a severe allergic reaction consisting of hives that began on her ears and then covered her body, with neck swelling, lymphadenopathy, joint pain and fatigue. She was treated with Benadryl and oral corticosteroids and an unspecified injection. Modafinil was discontinued on 2/28/03. The patient improved. This postmarketing case was reported by a nurse on 6/23/06.

Comment: The sponsor states this case is not consistent with multi-organ hypersensitivity reaction. However, there is skin, lymphadenopathy and joint involvement in addition to fatigue. I would not rule out a systemic hypersensitivity reaction without some laboratory evaluations (transaminases and CBC). I will include this case as a potential systemic multi-organ hypersensitivity reaction.

- **Upon review of Dr. Mannheim's review** of the pediatric ADHD submission, two more cases were discontinued because of rash. These two cases are included in a **Table in page 45 of Dr. Mannheim's review dated 9/29/2005, under the title: "Skin lesions identified in the vignettes of subjects leaving the trials because of an adverse event."**
 - Subject #13011 (study 207 B). An 8 year old male taking modafinil 100/200 mg, who developed leukopenia, abdominal pain, fever, and dry hives.

- Subject # 24004 (study 207 B). An 8 year old male taking modafinil 100/200 mg developed severe rash and leukopenia.

A summary of all pediatric cases of cutaneous reactions and potential multi-organ hypersensitivity reactions that lead to discontinuations in pediatric trials is presented in Table 1.

Table 1. Subjects with adverse reactions that lead to discontinuation and involved skin terms while taking modafinil in pediatric studies:

Case ID/Age/Gender/Adverse reaction	Dose (mg/d)	Onset (day)
Cases in which rash lead to drug discontinuation (d/c)		
# 020001- 12 F, "Non-serious" urticaria that required treatment with IV and oral corticosteroids.	?	13
Cases in which rash and some additional sign or symptom lead to drug d/c		
# 062338 – 7 M, rash, sore throat, fever diagnosed as SJS, or atypical EMM	425	15
# 18004 - 8 M, rash on cheeks, blister on lips, fever	200	14
# 056180 – 9 M, petechial rash, fever, swollen eyes, elevated transaminases Considered to have a multi-organ hypersensitivity reaction.	340	13
#315 – 11 F, fever, diarrhea, generalized pruritic rash, hospitalized for possible SJS later diagnosed as morbiliform rash.	200	4
# 18001 - 6 M, severe macular rash, fever, vomiting	200	3
#13011 - 8 M, fever, leukopenia, abdominal pain, dry hives	100/200	?
#24004 - 8 F, fever, rash and leukopenia	100/200	?

Comment:

This table lists eight pediatric cases, 5M/3F, ages 6 to 11 years of age. In addition to the case of SJS, seven children discontinued because of a rash alone or accompanied by fever, elevated transaminases, diarrhea or leukopenia. Some of these cases are consistent with early SJS or an early systemic hypersensitivity reaction. All but one of these cases (# 056180) occurred in modafinil-treated subjects in placebo-controlled trials. No such reactions were observed in placebo-treated subjects.

Although only one case of possible SJS (or atypical EMM) and one multi-organ hypersensitivity reaction ended up being considered clinically relevant by the sponsor, there is a strong signal for cutaneous and systemic hypersensitivity reactions in the pediatric database.

2. Review of December 19, 2006 submission.

On October 26, 2006, Cephalon met with the DPP and the DNP to discuss the rash associated with modafinil use in subject # 062638. The sponsor argued that this case represented atypical erythema multiforme major (EMM), an entity that may be drug-related but is distinct from SJS and has a more benign course. Additionally, Cephalon

stated that considerable experience with modafinil in both the US and Europe did exist, with no signal for SJS in adults (and no signal for SJS in children in Europe) arguing against a risk for SJS that would preclude approval in the pediatric population. ~~_____~~

b(4)

At the meeting, the FDA had the following recommendations to the sponsor:

- 1) Be sure that the Agency thoroughly understands the European experience with modafinil (providing data regarding both modafinil usage - by age if possible - and cases of serious skin reactions)
- 2) Provide updated analyses of US data using both exposure data (by age) and data regarding post-marketing cases of serious skin reactions
- 3) Explore further the differences in susceptibility to drug-induced SJS between adults and children
- 4) Discuss the differences in modafinil metabolism between pediatric and adult patients

The December 19, 2006 submission addresses the FDA request of October 26, 2006 and constitutes a major amendment to the Complete Response to NDA 21-785 (Nuvigil) AE letter of April 28, 2006 (submitted June 30, 2006) for the adult indications. It does not constitute a Complete Response to the NA actions for NDA 20-717s-019 (Sparlon for ADHD) ~~_____~~ The sponsor's responses to additional FDA informational requests (January 16 & 19, 2006 and February 7, 13, 23, and 27, 2007) are incorporated into this review.

b(4)

The FDA requests were addressed as follows:

- 1) **To be sure that the Agency thoroughly understands the European experience with modafinil (providing data regarding both modafinil usage [by age if possible] and cases of serious skin reactions).**

The sponsor provided background information from European studies and registries (two completed case-control studies and two ongoing registries) on Severe Cutaneous Adverse Reactions (SCARs).

Of note, some experts believe that (EM), SJS and TEN belong to a spectrum of the same condition. Other experts believe that EM, including EMM (a severe form of EM) is distinct from SJS and TEN and it can be differentiated based on the patterns, areas of involvement and the extent of the rash (see Table 1).⁵ The histopathology of cutaneous lesions of EM major [or Stevens Johnson Syndrome] principally resembles that of EM minor, but differs due to the much greater epidermal injury.⁶ Of note, the SCAR study showed that approximately 30% of cases of atypical EMM were associated with drug exposure, as compared to approximately 60% of SJS cases.⁵ Mortality rate associated with SJS and TEN is 5-15% and 40%, respectively.⁴

⁵ Auquier-Durant A, Mockenhaupt M, Naldi L, et al. SCAR Study Group. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson Syndrome and Toxic Epidermal necrolysis: results of an international prospective study. Arch Dermatol; August, 2002.

⁶ Fitzpatrick's Dermatology in General Medicine, 6th Edition, 2003

Table 2. Serious Cutaneous Adverse Reactions classification⁵

Diagnostic Category	Pattern of Lesions	Distribution	Extent of Blisters/ Detachment (%)
Erythema multiforme majus (EMM)	Typical targets, raised atypical targets	Localized (acral)	<10
Stevens Johnson syndrome (SJS)	Blisters of macules, flat atypical targets	Widespread	<10
Overlap SJS/TEN	Blisters of macules, flat atypical targets	Widespread	10-29
Toxic epidermal necrolysis (TEN) with spots	Blisters of macules, flat atypical targets	Widespread	≥30
Toxic epidermal necrolysis (TEN) without spots	No discrete lesions, large erythematous areas	Widespread	≥10

Source: Table 1, 12/19/06 submission. Original source: SCAR study.⁵

A summary of the characteristics of European databases for SCARs is presented in Table 3. Results of the RegiSCAR study were not available at the time of the 12/19/06 submission.

Table 3. European studies and registries on Severe Cutaneous Adverse Reactions (SCARs)

Study	Description	Reactions collected	Status
SCAR	International case-control study.	SJS ¹ , TEN ²	Completed. Preceded modafinil marketing
EuroSCAR	European case control surveillance. Cases: SCARs requiring hospitalization. Controls: patients hospitalized for acute conditions.	AGEP ³ , SJS, TEN	Completed in 2001
RegiSCAR	European registry of SCARs with collection of biological samples.	AGEP, SJS, TEN, DRESS ⁴	Ongoing since 2003, but validated info not available
German SCAR registry ⁵	Population-based registry of patients hospitalized for SCARs	SJS, TEN, EMM ⁵	Ongoing since 1990.

¹SJS: Steven-Johnson Syndrome; ²TEN: Toxic Epidermal Necrolysis; ³AGEP: acute generalized exanthematous pustulosis; ⁴DRESS: Drug reaction with eosinophilia and systemic symptoms. ⁵EMM: erythema multiforme major. ⁵Dokumentationszentrum schwerer Hautreaktionen (dZh).

The following section summarizes the methodology and findings of the EuroSCAR and German SCAR registry. For additional details on these studies, the reader is referred to **Dr. La Grenade's review (OSE/DDRE)**.

- Methodology used for the EuroSCAR study and German SCAR registry

For the EuroSCAR study, the clinical course of each potential case was abstracted from the hospital record, and the potential cases and their matched controls were interviewed by trained physicians or pharmacists in the hospital, filling out an extensive questionnaire. For the German SCAR study, potential cases were reported directly to the

registry. When inclusion criteria were met, a physician arranged a visit to the hospital and conducted the questionnaire. Cases were reviewed by an independent expert committee twice a year. Using clinical data, photographs and histopathology (when available), on the basis of a consensus definition developed by an international group of SCAR experts (presented in Table 1 of this review), cases were classified as "definite," "probable," or "possible" severe skin reactions, or were excluded. The analyses were **generally confined to cases classified as "definite" or "probable" by the dermatologic expert committee.** Drug exposures were examined with reference to the probable index-day. Whenever a patient started taking a drug, the patient was considered exposed only if this drug was taken in a "window" of 7 days preceding the index-day. For drugs with long elimination half-lives, the exposure window was extended to either 14 or 21 days as appropriate. For modafinil, a 14-day window was used.

- Results of the EuroSCAR and German SCAR Registry

The EuroSCAR study database covered a population of approximately 100 million people, with an estimated modafinil exposure of 15,500 unique patients. This database included total of 379 validated cases of definite or probable SJS, SJS/TEN-overlap, and TEN, from March 1997 through December 2001 (for all drugs). Among validated cases, exposure to modafinil within 2 weeks prior to the index-day was not found.

The German SCAR registry covered a population of approximately 82 million people, with an estimated modafinil exposure of 12,000 unique patients, between March 1997 and December 2005. This database included a total of 1039 cases of severe skin reactions validated as definite or probable. Of these, 387 were classified as SJS, 273 as EMM, 251 as SJS/TEN-overlap, 99 as TEN, and 29 as EMM/SJS not further distinguishable. Among validated cases, exposure to modafinil within 2 weeks prior to the index-day was not found.

Comment:

As per the sponsor's analyses, among the validated cases of definite or probable EM/SJS, no exposure to modafinil was found within two weeks of the index date in neither study. Rather than looking only at cases that fit the classification of "definite" or "probable" and cases that occurred only within 2 weeks of the index date, it seems relevant to look at all cases that were severe enough to warrant evaluation regardless of time to onset of the event. On 1/19/06, the FDA asked Cephalon to provide a summary table and narratives of all SCARs reported with modafinil in these two trials, including those that were not considered to be definite cases and those that occurred beyond 2 weeks of starting therapy.

On February 7, 2007, the sponsor provided re-analyses of all SCARs from the EuroSCAR, German SCAR registry as well as results of the RegiSCAR study, including cases without expert validation, regardless of time to onset of the event. There was no exposure to modafinil for any of the SCARs found in these three studies. There was,

however, a possible case of TEN with adrafinil, a structurally related compound (CIOMS report 20010027).

This submission also provided updated exposure information for these three studies, including exposure broken down by age (0-18 years and >18 years). Exposure in these studies is presented in Table 4. The methodology for ascertainment of cases in the RegiSCAR study was similar to that of the EuroSCAR and German SCAR studies.

Table 4. EuroSCAR, RegiSCAR and German SCAR Registry Exposure (Unique patient counts)

STUDY (Study Period)	EuroSCAR (Apr 1997-Dec2001)	RegiSCAR (Jan 2003-present)	German SCAR Registry (Jan 1999-present)
PSUR Periods	01-Feb-98 to 30-Sep-01	01-Mar-03 to 31-Aug-06	01-Apr-99 to 31-Aug-06
Patient Treatment Days	3,301,241	6,704,716	1,675,088
Total Patients	25,591	51,975	12,985
Adult Patients	24,798	50,364	12,582
Pediatric Patients*			
ADJUSTED FOR COVERAGE**			
Total Patients	15,548	31,446	11,687 = 57,681 Total
Adult Patients	15,066	30,471	11,325
Pediatric Patients	482	975	362 = 1,819 <19 years

b(4)

Source: Table 2 of February 7, 2007 response.

* The ratio of ~~-----~~ was used to derive the total pediatric patients within this table. ~~-----~~ is the pediatric use in the US as per Verispan Source of Business Audit™ (See section 2.a of this review)

** Periodic Safety Update Report (PSUR) exposure data by average treatment duration corrected for coverage rate per country (%).

Comment:

The finding of no cases of serious skin reaction associated with modafinil within these three studies should not come as a surprise because the size of the database is relatively small. An estimated exposure to modafinil of approximately 58,000 patients (all ages, including 1,800 pediatric patients) is inadequate to evaluate an event with a background rate of 1-2/million patients per year. Additionally some cases may have not been captured, as not all hospitals participated in these studies (hospital participation varied from 30% in Italy to 90% in Germany). Moreover, the EuroSCAR and RegiSCAR did not include cases of Erythema Multiforme Major (EMM). Of note, 25% of severe cutaneous reactions in the German SCAR registry were EMM; therefore, the RegiSCAR and EuroSCAR may have missed a substantial number of serious skin reactions. The German SCAR included EMM but did not include acute generalized exanthematous pustulosis (AGEP) which was included in both the RegiSCAR and EuroSCAR, or drug reaction with eosinophilia and systemic symptoms (DRESS), which was included in the RegiSCAR only.

2) Provide updated analyses of US data using both exposure data (by age) and data regarding post-marketing cases of serious skin reactions.

2.a Updated modafinil exposure information (including exposure by age)

The sponsor presented the estimated patient exposure to modafinil in the US and Worldwide from launch (September 1994) through August 2006, in two ways: 1) Patient-years of treatment and 2) Unique patients, using two different approaches. The sponsor's estimated overall exposure to modafinil is approximately **925,000 patient years (PYRs) or 2.6 million Unique Patients**. Results of these estimations are summarized in Table 5. Modafinil exposure by age is presented in Table 6 (US only).

Table 5. Estimates of exposure to modafinil (all ages) from September 1994 through August 2006, US and Worldwide.

	Patient-treatment years (PYRs) ¹	Unique patients (two approaches)	
		Using Verispan ² data (ONLY US)	Using independent estimate of average treatment duration ³
United States			2,283,250
Europe			264,467
Rest of world			70,538
Overall			2,618,255

b(4)

¹ Patient treatment years (PYRs) were estimated using IMS data by

² Verispan Source of Business Audit data available from Jan 2002 and beyond (US only). To estimate US patient counts between 1999 and January 2002, a back-extrapolation of the Verispan data was performed by

³ Estimated from total number of patient-treatment days (derived from estimation of PYRs) divided by the estimated average duration in days. The average duration of days was derived from an independent longitudinal study ("patient-level data from Wolters Kluwer, multinational publisher and information services company") and was 129 days.

Table 6. Sponsor's estimation of modafinil exposure for different age groups in the US¹ (January 1999-August 2006)

	PYRs	Unique patients (Verispan approach)
All		
Pediatric (≤ 18 years)		
Adult		

b(4)

¹ Pediatric and adult counts were estimated using the average ratio of pediatric to adult patients in Verispan reports from 2002-2006, applied to estimates of exposure in the total population (from Table 5, above). Source: Sponsor's December 19, 2006 submission.

Comment:

*Although the usual practice in epidemiologic estimations is to use patient years of exposure as the denominator to evaluate risk, given the fact that SJS is much more common within the first few weeks of therapy, the use of the unique number as the denominator for patients exposed to modafinil appears to be a reasonable approach. Depending on the approach, the number of unique patients exposed to modafinil in the US is approximately _____ (Verispan extrapolation) or **2.3 million** (alternative approach). Of note, there are no details of the methodology used for the extrapolation of Verispan data and no datasets have been provided to confirm these analyses. For the alternative approach, the sponsor used an "independent longitudinal study" using a source from which we have very limited information.*

b(4)

Additional analyses of use data for modafinil in the US were provided by OSE/DSRCS, using Verispan™ Total Patient Tracker (Provided by Carol Pamer, Drug Use Specialist). Without taking into consideration mail order prescriptions, the number of Unique Patients exposed to modafinil from January 2002 through December 2006 was approximately _____ of whom _____ were <19 years old, which is not inconsistent with the sponsor's estimation. The exposure in patient years was _____ of whom _____ were for ages <19 years. ²

b(4)

2.b Provide updated data regarding post-marketing cases of SCARs

Cephalon reviewed its modafinil pharmacovigilance database to identify all reported cases of SJS from the date of the original product launch in France in September 1994 through 31 October 2006. There were no cases of SJS or SJS/TEN from outside the US. In this submission, the sponsor identified one new case of SJS/TEN and one systemic hypersensitivity reaction. These cases are summarized below:

- Case US016856 (includes initial information as well as follow up information from hospital records, submitted 2/23/07), a 17 year old female, who was taking lamotrigine (since October 2005) and amoxicillin/clavulanic acid (unknown duration), initiated modafinil 300 mg/d on November 14, 2005. On _____ she developed fever and extensive rash, with mucosal membrane involvement, requiring hospitalization and IVIG therapy. Both drugs were stopped. One month later she received modafinil 50 mg and within 3 hours she developed a rash. The rash, however, was milder than before. Skin biopsy was not available. She was not rechallenged with lamotrigine.

b(6)

The case was diagnosed as SJS, probably related to lamotrigine, as it is well known that lamotrigine is associated with severe skin reactions. However, the most recent medication introduced to the patient had been modafinil, therefore, this reaction is also consistent with modafinil-induced SJS. Positive re-challenge with modafinil is supportive of modafinil as the causative agent.

- Case US017511, a 46 year old female, developed a maculopapular skin rash, fever and elevated transaminases on day 8 of modafinil treatment (See Appendix 1). The rash was not thought to be SJS but the case is consistent with a multi-organ

hypersensitivity reaction. This case had been submitted as part of the June 30, 2006 submission.

Both these cases occurred in patients taking lamotrigine. Another potential case of systemic multi-organ hypersensitivity reaction submitted on June 30, 2006, (subject # US 0138995064) was a patient who was on lamotrigine when the event occurred. The possibility of a drug-drug interaction between lamotrigine and modafinil was discussed with Dr. Ta-Chen Wu, Clinical Pharmacology reviewer. Data suggest that modafinil moderately induces CYP3A4 activity.⁷ Available data cannot rule out a drug-drug interaction (e-mail communication, 2/27/2007).

Upon discussion of these cases with the OSE/DDRE safety evaluator (Charlene Flowers), it came to our attention that case # US15856 (17 y.o. with SJS) had been submitted to MedWatch as a periodic report instead of an expedited report, and that an additional case of TEN associated with modafinil (case # US019026) had been reported to MedWatch, but was not included in the **sponsor's December 19, 2006 submission**. Subsequently, on February 7, 2007, at the request of the FDA, Cephalon submitted all reports (serious and non-serious) of SJS/TEN and skin related reactions that occurred after October 31, 2006 (the cut-off date for the December 19, 2006 submission).

The February 7, 2007 submission includes case # US019026 as follows:

- Case US019026, a 49 year old woman with systemic lupus erythematosus, initiated Provigil 200 mg on 11/3/06. ~~_____~~ later, she was diagnosed with TEN and was hospitalized in a burn unit. For more details, see Appendix 1.

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This is a complex case; however, the treating physicians considered the event to be likely related to Provigil as it was the only new medication added to the patient's medical regimen. Of note, the biopsy results were read by the dermatopathologist as Erythema Multiforme Major. The pathology of EMM is indistinguishable from SJS and TEN.³ Clinically, the patient had TEN. The skin biopsy grew Staphylococcus aureus; however, this is a common organism in the skin flora and it does not mean that it was infected.

In addition to this case, this submission included the following non-serious skin reaction as follows:

- Case US019005, a 46 year-old male, initiated Provigil 200 mg daily on 12/2/06. ~~_____~~ later the patient reported to the prescribing physician that he had hives on his back, legs and buttocks and blisters around his mouth and that he was going to the emergency room for evaluation. He was not taking other medications at the time. Provigil was discontinued and steroids were prescribed at the ER, previous to his **release. The patient's wife** stated that all symptoms resolved within 24 hours.

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⁷ Modafinil labeling. Pharmacokinetics, Metabolism and elimination.

This case was described as non-serious urticaria/hives. However, it required modafinil interruption and immediate treatment. Contrary to SJS/TEN, urticarial rashes are Type I hypersensitivity reactions.

2.c Estimation of Reporting Rates

As part of the February 7, 2006 response to the FDA request for information, Cephalon acknowledges a total of 3 cases of SJS/TEN for modafinil (*It is unclear which cases the sponsor is accepting*). Based on a background incidence of 1/1,000,000, Cephalon states that they **“are not seeing more events for modafinil than expected.”**

This reviewer disagrees with the sponsor’s assessment. As of December, 2006, there were **six cases of severe cutaneous reactions (EMM, SJS, and or TEN) and eight potential multi-organ drug hypersensitivity reactions in the postmarketing database.**

A summary of all SCARs and potential multi-organ hypersensitivity drug reactions in the postmarketing database is presented in Table 7. More extensive narratives of these cases are presented in Appendix 1.

Of note, SCARs are often associated with fever, constitutional symptoms and internal organ involvement. Leukopenia/lymphopenia and mild elevation of liver enzymes are common in SJS and TEN. Overt hepatitis is observed in 10% of cases of SJS.⁴

Multi-organ drug hypersensitivity reactions involve internal organs and may present as nephritis, pneumonitis, hepatitis, etc. Systemic reactions may also involve the hematologic system, occasionally presenting as pseudolymphoma.

Lymphocytosis and atypical lymphocytes are common in DRESS. The term DRESS refers to a systemic reaction with prominent eosinophilia (70% of cases have absolute eosinophil count >1300 mm³). DRESS is also considered one of the SCARs.⁴ The mortality rate for DRESS is 10%.⁴

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Table 7. Listing of severe cutaneous adverse reactions and potential multi-organ drug hypersensitivity reactions in modafinil's postmarketing database.

<ul style="list-style-type: none"> • Severe cutaneous reactions (n=6) ISR# 3882684 – 27 F, SJS (history of SLE) ISR#5206823 – 17 F, SJS (patient was on lamotrigine)(+ rechallenge) ISR# 4831856 - 68 F, EMM ISR# 4896253 - 42 F, SJS/TEN (patient was on escitalopram) ISR# 4677929 - 54 ? SJS/TEN (limited information, patient died) ISR#5194832 – 49 F, TEN (history of SLE, on celecoxib and duloxetine) 	Onset 1 day 2 weeks 2 weeks 2 weeks ? 3 weeks
<ul style="list-style-type: none"> • Potential multi-organ drug hypersensitivity reactions (n=8) ISR# 5013599: 31 F, rash, eosinophilic myocarditis, death. (Patient was on oxcarbazepine.) ISR/#5060040: 15 M, rash, fever, fatigue, petechia, worsening renal function, eosinophilia (diagnosed as DRESS syndrome) US# 017511: 46 F, rash, fever, elevated transaminases (patient on lamotrigine) US# 0138995064: 25 F, fever, nausea, confusion, presumptive meningitis, petechial rash (patient on lamotrigine) + rechallenge US# 016358: 41 F, fever, petechial oropharyngeal rash, thrombocytopenia, +ANA, diagnosed as SLE at the time of the event. US# 009180: 61 M, fever, nausea, weakness, hyperbilirubinemia, splenomegaly, pancytopenia, history of hepatitis C, died of “lympho proliferative disease” US# 012767: 38 M, back and flank pain, fever, chills and rash, elevated transaminases (history of HIV infection and tuberculosis) US# 010763, 22 F, hives, neck swelling, lymphadenopathy, joint pain and fatigue. 	3 days 5 weeks 8 days 3 months 2 days 2 days 11 days 1-2 days

This table does not include the case of the 7 year old with SJS from the pediatric trial.

Some postmarketing cases were confounded by the use of concomitant medications that have been associated with SCARS (e.g. lamotrigine (n=3), celecoxib/duloxetine (n=1) oxcarbamazepine (n=1)). However, there was a temporal association between the initiation of modafinil and the onset of the serious rash and modafinil had been the most recent drug introduced to the patient.

Comment:

The multi-organ hypersensitivity reactions are particularly difficult to analyze because of the lack of complete data and multiple differential diagnoses. For instance, one patient (US016358) was diagnosed with systemic lupus erythematosus (SLE) at the time of the reaction. However, there is no follow up information regarding whether the patient really developed SLE. (One patient with TEN also had a history of SLE, treated with prednisone and azathioprine [ISR#5194832]). Another patient was reported to have died of a lymphoproliferative disease (# US009180), but there is no documentation of such diagnosis.

Two patients had a positive rechallenge to modafinil. Subject ISR# 5206823, who was also on lamotrigine, who presented with SJS while receiving modafinil 300 mg, developed a mild skin rash when a low dose of modafinil (50 mg) was introduced. Patient # US 0138995064, who had been hospitalized for fever, nausea, confusion and presumptive meningitis while taking modafinil, was also on lamotrigine. After discharge,

she developed fever and vomiting within minutes of taking one dose of modafinil. The positive rechallenges support a causative role for modafinil.

Table 8 shows the estimated the reporting risk of EMM, SJS and TEN in the US from January 2002 through December 2006 (the period from which Unique Patient data are available).

Table 8. Reporting risk and reporting rate of SCARs with modafinil 2002-2006

Age group	Total Patient Tracker Aggregate (%) ¹	Total SCAR (SJS/TEN only) cases 2002 – 2006 in AERS	Reporting risk / million patients	PYRs (Total prescriptions dispensed/12)	Reporting rate/million PYRs (SJS/TEN only).
All		6 (5)	4.9 (3.5)		9.0 (7.5)
0-18 year		1(1)	17.4 (17.4)		52.5 (52.5)
> 18 year		5(4)	3.7 (2.9)		7.7 (6.2)
Unknown					

b(4)

¹ Verispan™ Total Patient Tracker. Total number of unique patients who filled a prescriptions at a retail pharmacy in the US (does not include mail orders). Verispan™ VONA: Total prescriptions dispensed by retail pharmacies in the US (does not include mail orders). 2002-2006. Provided by Carol Pamer, OSE/DSRC, Drug Use Specialist. Data extracted 1/30/2007.

Comment:

*An analysis using patient years of exposure from 1998 thorough 2006, instead of 2002-2006, using rigorous case criteria for the diagnosis of SJS and TEN was conducted by Dr. La Grenade (epidemiologist from OSE/DDRE). This conservative analysis included 4 patients (ISR# 4193236, 4896253, 5206823 and 5194832). The reporting rates in her analyses were **5.7 per million PYRs for patients of all ages and 36 per million PYRs for patients ≤ 18 years old, which is not very different from my analysis.** For details on this analysis see OSE/DDRE, CMC# 2007-169.*

In summary, the overall reporting rate of SJS/TEN with modafinil in the postmarketing database (7.5 per million PYRs) is above the background rate of SJS (1-2 per million PYRs). Given the known phenomenon of under-reporting of spontaneous events, these numbers are of concern. This reporting rate is higher in children and adolescents ≤ 18 years of age (52 cases per million PYRs), based on a single case in a 17 year old female. Using the age of 16 years as the cut-off age for analyses, there are no postmarketing cases of SJS or TEN in the pediatric population (although there is a case of DRESS in a 15 year old). However, the postmarketing database in ≤ 18 years is relatively small for adequate evaluation of these events (56,000 subjects at the most). Therefore, the current analysis of postmarketing events does not rule out the possibility - suggested in the pediatric clinical trials - of a high risk of severe cutaneous and multi-organ hypersensitivity reactions in children.

3) Explore further the differences in SJS between adults and children

The sponsor conducted a review of the literature and found no specific research that addresses whether there is a differential risk for SJS in children and adults. Their review of published case series found a total of 65 cases of SJS/TEN in children. The products more commonly associated with SJS/TEN were sulfonamides, anticonvulsants, non-sulfonamide antibiotics and NSAIDs. A separate retrospective review of cases of bullous EM, SJS and TEN from the Hospital for Sick children in Toronto from 1984 through 1995 included 61 cases which involved similar drugs to the ones described in the sponsor's analyses.

The sponsor argued that as some drugs are differentially prescribed in children and adults, the relative frequency of their association with SJS would be expected to be different to some extent and concluded that medications that are implicated in childhood SJS/TEN are also implicated in the etiology of adult SJS/TEN. The Sponsor did not find any examples of differential risks in children versus adults, provided that a particular agent was used in both populations.

Comment:

Some epidemiologic data suggests that SCARs are more common in children than in adults taking antiepileptic drugs as compared to adults. As per Dr. Racoosin's review (dated 1/14/04) of the German Registry related to NDA 20-241, Lamictal, the estimated frequency of SJS/TEN per 10,000 prescriptions for ages ≤ 15 years and >15 years were as follows: for carbamazepine, 0.13 and 0.04 cases, respectively; for lamotrigine, 0.20 and 0.14 cases respectively; for Phenobarbital 0.08 and 0.02 cases, respectively, and for phenytoin, 0.56 and 0.13 cases, respectively.

Labeling for Lamictal™ (lamotrigine) includes a Box Warning for serious skin rashes, as follows: "The incidence of these rashes [serious rashes requiring hospitalization and discontinuation of treatment] which have included SJS, is approximately 0.8% (8 per 1000) in pediatric patients (age <16 years) receiving Lamictal as adjunctive therapy for epilepsy and 0.3% (3 per 1000) in adults on adjunctive therapy for epilepsy."

Therefore, it seems that severe skin reactions occur two to ten-fold more often in children than adults receiving antiepileptic drugs.

In summary: The sponsor found no evidence in the literature that a differential risk of SJS exists between children and adults. Data from the German SCAR registry (from a previous submission to the Lamictal NDA) and data from lamotrigine clinical trials suggest that the risk of serious skin reactions is 2-10 folds greater in children as compared to adults taking anticonvulsants. This pattern is not observed with modafinil if we use 16 years as the cut-off age for analyses.

4) Discuss the differences in modafinil metabolism between pediatric and adult patients.

The sponsor acknowledges that there are some differences in pharmacokinetic parameters between pediatric and adult patients.

The estimated half-life ($t_{1/2}$) for the youngest patients studied (aged 6 to 7 years) is approximately 7 hours. The $t_{1/2}$ increases with age up to the ages of 9 to 11 years (which coincide with an approximate 30-kg body weight).

Light children (<30 kg) require lower doses of modafinil than children >30 kg and adults. The dose needed to achieve a clinically relevant effect ($AUC = 150 \mu\text{g}\cdot\text{hr}/\text{mL}$) for patients weighing <30 kg is 340 mg and for patients weighing 30 kg or more is 425 mg. A comparable exposure is achieved with a 400 mg dose in adults.

The rate of modafinil metabolism is higher in children and adolescents as compared to adults. The higher rate of metabolism is associated with higher plasma concentrations of the sulfone metabolite.

Despite these differences, the sponsor reports that the plasma maximum concentration (C_{max}) of modafinil and modafinil sulfone in patient # 062338 on the day of the adverse event was in the lower range concentration spectrum compared to other pediatric (phase 3 ADHD studies, $n=411$) and adult subjects (clinical pharmacology studies, $n=55$). (No datasets have been provided.)

Additionally, as part of the ADHD program the Sponsor conducted a 4-week oral toxicity study of modafinil sulfone in rats. The study suggested that the higher concentration of modafinil sulfone is not associated with greater or unique toxicities.

As part of this submission, Cephalon argues that the speculative association of modafinil sulfone with arylsulfonamide antibiotics or arylsulfonamide nonantibiotics is erroneous, from the chemical and metabolism perspective, as neither modafinil sulfone nor its parent contains the unique moiety required for chemical classification as a sulfonamide, nor can either be metabolized to this functional group.

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The Chemistry reviewer, David Claffey, **agrees with the sponsor's statement that modafinil's metabolite is a sulfonyl amide not a sulfonamide and that it lacks the usually present in drugs that cause hypersensitivity reactions.**

b(4)

Comment:

Idiosyncratic hypersensitivity reactions may occur with "normal range" C_{max} of a drug/metabolite. The lack of toxicity in a 4-week rat study of a drug/metabolite does not preclude hypersensitivity reactions in humans. Structural analyses are not sufficient to disprove drug toxicities for any drug.

5) Review of FDA consultant's conclusions and recommendations

Excerpts from Drs. Luke and La Grenade's reviews are presented/summarized below:

- **Dr. Luke** (FDA, DDDP dermatologist, 2/14/07 review):
 - The case # 311/062338 from the pediatric clinical trial cannot be considered a **“definite” case of SJS. However, there is not sufficient information to exclude** the possibility that this case may be one of SJS. The splitting of the diagnosis to encompass **“atypical” EMM is a semantic point that has roots in one study done in Europe** that lacks the racial and drug use demographics seen in the US. Further, the case and its ramifications should be taken in context of the post-marketing surveillance data in consideration of the adult treatment and dosage with modafinil for any labeling proposals for modafinil.
 - There is no data to support whether the R-enantiomer has a better or worse safety profile with regard to cutaneous adverse events than the enantiomeric mixture.

Recommendations:

Modafinil and armodafinil (if and when approved) should carry appropriate warnings with regard to risk of severe cutaneous and mucosal adverse events such as SJS or EMM. The context of the warning depends on the risk vs. benefit evaluation and the review division should make the decision as to the extent and location in the labeling of such a warning.

- Careful evaluation of any differential risk of armodafinil (R-enantiomer for modafinil) should be conducted, either as part of pre-market or post-market study (e.g., a prospective data safety monitoring program or a study specifically designed to tease out such risk).
 - Evaluation of risk for severe skin rash for either drug is especially needed if there is any proposed use in a pediatric population, where risk of severe cutaneous, mucosal, or other adverse events may have a differential risk from that in adults.
- **Dr. La Grenade** (OSE/DDRE dermatologist and epidemiologist, 3/8/07 review):
 - The EuroSCAR data provided by the sponsor are insufficient to rule out an association between modafinil exposure and SJS/TEN because modafinil exposure is relatively low, the EuroSCAR excludes hospital acquired cases of SJS/TEN, which account for approximately 33% of all cases, and population coverage in EuroSCAR countries varies from ~ 30 % to just over 90%.
 - In addition to one case of SJS/TEN from a clinical trial, there were 4 spontaneous report cases consistent with a diagnosis of SJS/TEN. These cases support an association between modafinil use and SJS/TEN, particularly in children.
 - Even if we accept the diagnosis of atypical EMM in case 062338, there is still a 30% association with a drug induced etiology.

Recommendations:

More data on the possible risk of SJS/TEN in children should be collected and studied before approval for indications in pediatric populations.

6) Review of rashes in the armodafinil pre-marketing program. Comparison to the modafinil database. (Not part of the 12/19/06 submission)

It is unknown whether the risk for severe hypersensitivity reactions with armodafinil is the same or different than for modafinil. No cases of SCARs or multi-organ drug hypersensitivity reaction were observed in the modafinil and armodafinil pre-marketing database in adults. All potential cases of serious skin/hypersensitivity reactions were in the modafinil pediatric trials, and of those, only one was thought to be consistent with SJS, and one with a multi-organ hypersensitivity reaction. No pediatric data are available for armodafinil from clinical trials, and no postmarketing data exist for armodafinil.

The rate of any rash with modafinil in adult trials was similar to placebo (approximately 2%). The rates of rash in adult armodafinil trials were 1%, 4% and 0.2% for the 150mg dose, 250mg dose and placebo, respectively. Of note, the incidence of rashes was higher in the Non-white (5%) as compared to White (1%) patients. Ethnicity has been recently brought up as a factor that may affect the incidence of serious skin reactions.

There was only one serious skin reaction in the entire armodafinil database. This was a case of serious urticaria with angioneurotic edema in a patient with narcolepsy, on Day 16 of armodafinil 250 mg (subject # 0441026). Additionally, there was one case of **"hypersensitivity reaction, dysphagia and bronchospasm" on Day 11 of armodafinil** treatment in a patient with history of sensitivity to multiple medications including sulfa, penicillin, demerol, fluoxetine and bupropion (subject # 1884236). This case is consistent with an anaphylactoid reaction.

Comment:

Urticaria and angioneurotic edema are Type I hypersensitivity reactions, while SCARs are mostly Type IV delayed hypersensitivity reactions. Other "anaphylactoid" mechanisms leading to direct or non-specific liberation of histamine or other mediators of inflammation are also common for drug reactions.⁴ The rate of angioedema in the armodafinil database (1/1595=0.06%) is close to that of the ACE inhibitors (2-10 per 10,000 new users, or 0.02 to 0.1 %²).

b(4) b(5)

7) Updated exposure in Modafinil and Armodafinil databases

The exposure to modafinil in pediatric clinical trials and the exposure to armodafinil in pre-marketing adult clinical trials are presented in Tables 9 and 10. Cephalon submitted this information at the FDA request on March 21, 2007.

Table 9. Pediatric exposure in modafinil clinical trials database

Age (years)	Controlled trials		All trials
	Placebo	Modafinil	Modafinil
6-11	260	536	1003
12-17	128	293	619
6-17	388	856	1622

Note: Controlled trials include ADHD studies 207, 213, 309, 310, 311 and Excessive Sleepiness studies 3027 (narcolepsy), and 3028 (OSA)

Table 10. Exposure to armodafinil in pre-marketing clinical trial database

	Controlled trials		All trials
	Placebo	Modafinil	Modafinil
All patients	471	724	1595

Additionally, in March 16, 2007, in response to an FDA informational request, Cephalon submitted an update of serious skin/hypersensitivity reactions from January 2006 (the cut-off date of the June 30, 2006 Complete Response) through present. There were no cases of serious skin or systemic hypersensitivity reactions with armodafinil for this period.

8) Conclusions

This review addresses several questions raised by the FDA in a meeting with Cephalon held on October 26, 2006. The data reviewed indicates a relationship between the use of modafinil and the onset of serious hypersensitivity reactions, including erythema multiforme major (EMM), Stevens-Johnson syndrome (SJS), toxic epidermic necrolysis (TEN) and multi-organ hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS).

- Clinical trial data

The review of the modafinil clinical trial database suggests a higher risk of serious skin and multi-organ hypersensitivity reactions in the pediatric population as compared to adults.

- Pediatric clinical trials (n=1622 exposed to modafinil in controlled and open label studies)

One case of SJS (or atypical EMM), in a 7 year-old male on Day 15 of modafinil treatment was observed in the pediatric trials. The estimated crude rate of SJS in this database is $1/1622 = 0.06\%$. The background rate of SJS is 1-2 cases per million PYRs of exposure and it is associated with 15% mortality. (Even if this is a case of atypical EMM, as sustained by Cephalon, the diagnosis is not completely benign.)

In addition to this case, seven subjects, ages 6 to 12 years, presented with a cutaneous reaction that required discontinuation, sometimes with hospitalization – rash alone or accompanied by fever (n= 4); elevated transaminases (n=1) or leukopenia (n=2) - suggesting early SJS or multi-organ hypersensitivity reactions. No adequate clinical or laboratory follow up information was available in most of these cases. The crude rate of skin reactions requiring discontinuation, including the case of SJS, was 8/1622= 0.5%. No such cases occurred in children receiving placebo.

- Adult clinical trials (n=4178 in controlled and open label studies)

No serious skin or multi-organ hypersensitivity reactions were observed in adult subjects in modafinil trials.

- Postmarketing database (1.8 million unique patients from 1999 through August 2006 in the US; 2.6 million unique patients from 1994 through August 2006 worldwide)

No cases of Severe Cutaneous Adverse Reactions (SCARs) were found in the EuroSCAR, the RegiSCAR, and the German SCAR registry. These studies cover approximately 58,000 subjects exposed to modafinil, of whom approximately 3% were <19 years of age. The lack of cases of SCARs in the European postmarketing databases is not reassuring as the estimated exposure to modafinil in these databases is too small to address uncommon events such as SJS and TEN, particularly for the pediatric population (approximately 1700 subjects).

Six SCARs and eight potential multi-organ hypersensitivity reactions were identified in the modafinil postmarketing database as of February 2007. All cases were domestic. Most of the postmarketing cases were confounded by concomitant medications (lamotrigine, n=3; oxcarbamazepine, n=1; celecoxib, n=1), or comorbidities (systemic lupus erythematosus, n=2; HIV+, n= 1) and contained limited/insufficient information. However, there was a temporal relationship with modafinil use for all of the cases, with two cases of positive re-challenge, which is supportive of a causal association (see Appendix 1).

The estimated use of modafinil in the US from January 2002 through Dec 2006 was ~~_____~~ PYRs or ~~_____~~ unique patients, of whom ~~_____~~ were <19 years of age.

b(4)

The reporting rate of SJS/TEN in AERS was estimated by Dr. Lois La Grenade, a dermatologist and epidemiologist in OSE/DDRE, using rigorous case definition criteria. In this conservative analysis that included only 4 cases (including a 17 year old subject), the estimated reporting rate of SJS/TEN through December 2006 was **5.7 cases per million PYRs for patients of all ages**, which is above the background rate of 1-2 cases per million PYRs reported in the literature. Given the known phenomenon of under reporting, this finding is of concern. For comparison, the reporting rate of SJS/TEN in AERS with celecoxib, a COX-2 selective non-steroidal anti-inflammatory drug (NSAID) has been estimated to be 6 cases per million PYRs, and for valdecoxib, another COX-2 selective NSAID, 49 cases per million PYRs. Of note, celecoxib carries a WARNING

for severe skin reactions, including fatal SJS and TEN. Valdecoxib was withdrawn from the market in 2005 in part because of these adverse reactions.

If we use a cut-off age of 16 years for the analysis of pediatric cases, there are no cases of SJS/TEN in this age group in the postmarketing database (although there was a case of DRESS in a 15 year old subject). The estimated exposure to modafinil in the pediatric population is relatively small — of the total exposure). Therefore the analysis of postmarketing events does not rule out the possibility of a higher risk of serious cutaneous reactions in the pediatric population that has been raised in the clinical trials.

b(4)

It is unknown how the risk of these serious adverse reactions with armodafinil compares to the rate observed with modafinil. There were no cases of severe cutaneous or systemic hypersensitivity reactions in the armodafinil clinical studies. There was a case of angioedema and one anaphylactoid reaction in the armodafinil database. The crude rate of angioedema in the armodafinil database is $1/1595 = 0.06\%$, a rate close to that of the ACE inhibitors.

9) Recommendations

This reviewer recommends:

1. Prominent location of the information related to serious skin and multi-organ hypersensitivity reactions with modafinil in the WARNINGS section of the Provigil and Nuvigil labels.
2. Collection of additional information to better address the benefit/risk ratio of modafinil before it is approved for use in the pediatric population. We concur with the need of a ~~_____~~ as previously recommended by the DPP.
3. Prominent information that Provigil (and Nuvigil) is not approved for use in children and adolescents
4. The sponsor needs to make an effort to improve the follow up of cases with serious skin and hypersensitivity reactions in ongoing and future clinical trials of modafinil and armodafinil, as well as in postmarketing reporting. Any ongoing or further studies with these drugs need to incorporate into the protocol an adequate follow up of these cases, including dermatologic evaluation, laboratories (CBC,

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transaminases), photographs, biopsy results, and if applicable, final diagnosis, treatment received, and information regarding clinical outcome.

5. A risk minimization plan (RMP). In addition to labeling changes, a RMP could include quarterly reports to the NDA (separate from the regular Periodic Reports or PSURs) of new cases of serious skin/hypersensitivity reactions, a Dear Healthcare Professional letter, educational materials for physicians and patients, etc.
6. Angioedema and anaphylactoid reactions should be included in the WARNINGS section of the label.

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Appendix - Cases of serious skin reactions with modafinil reported to AERS (Approval through OCTOBER 2006) as of February 6, 2007

ID	Yr	Age (Yrs) Gender	Diagnosis	Narrative //Comments
1 ISR# 3882684 US 016623 Triage 163459	2002	28 ?	EM (not SJS)	Began with itchy eyes, then skin and mouth eruptions consistent with Stevens Johnson's Syndrome. Hospitalized as unable to eat/drink. Biopsy results = erythema multiforme. Admitted discharged discharged the event was resolving.
2 ISR# 4193236 Triage 202048 US 016624	2003	27 F	SJS	Patient had 1 week history of sore throat which progressed to swelling of the oral cavity and difficulty swallowing; high fevers to 106.2 F on day of admission, and severe sloughing of the oral and vaginal mucosa. She has a history of Systemic Lupus. As per the sponsor, event occurred the first day of therapy. Information is incomplete.
3 ISR# 4376619 US 13240 C1538d/311/US/ 062338 (Clinical trial)	2004	7 M	EMM/SJS	This patient 7 year-old Caucasian male with a history of ADHD was enrolled a pediatric study protocol for modafinil. Fifteen days after the first dose of study medication, the patient reported a sore throat and a temperature of 101.9 degrees Fahrenheit, symptoms were consistent with streptococcal pharyngitis or Coxsackie viral infection. Additionally, there was a small rash on several areas on his body. The patient developed a significant severely itchy skin rash that involved most of his body. His lips were swollen, red and crusty, and he had difficulty urinating due to pain.
4 ISR# 4831856 US 010480	2005	68 F	EMM	A 68-year old female initiated modafinil therapy 200mg daily for the treatment of narcolepsy. Two weeks later, she experienced a sore throat, mouth swelling with ulcers and a rash over her body. The patient was admitted to the hospital for dehydration. The prescribing physician indicated that the events were possibly or probably related to Provigil therapy. She had widespread, blanchable, papular rash with pustules of the back, arms and legs. A biopsy revealed chronic perivascular dermatitis with marked basal layer damage, dermal-epidermal separation and epidermal necrosis. A diagnosis of erythema multiforme major was made. Provigil was suspected and was subsequently discontinued. The patient recovered and since that time, there had been no recurrence of the event.
5 ISR# 4896253 ISR# 5025114 US 016653	2005	42 F	SJS/TEN	A female patient initiated Provigil 100 mg daily and experienced Stevens-Johnson Syndrome, describing her experience as "skin falling off." Concomitant therapies were escitalopram (which has a WARNING for TEN) and risperidone. Approximately two weeks after first dose of modafinil, the patient experienced itching and black spots over her body which then progressed to a pimple-like rash. The symptoms continued despite use of an antihistamine. The patient was admitted to the hospital with a diagnosis of SJS and toxic epidermal necrolysis (TEN). Provigil was discontinued at this time, as well as, Lexapro and Risperdal. The psychiatrist attributed a likely causal relationship between the events and Provigil as this was the only new therapy recently introduced to the patient's medical regimen. A skin biopsy was obtained from the right shoulder revealing full thickness epidermal necrosis overlying re-

				epithelialized skin. The patient was recently examined a few days prior to this report and her overall condition continues to improve.
6	ISR# 4677929	2005	54? SJS/TEN (Death)	<p>Official cause of death was Spontaneous Subarachnoid Hemorrhage with other significant conditions contributing to death Sepsis and Toxic Epidermal Necrolysis. He had a rash covering his entire body, limbs, face, hands and feet, which went untreated or investigated for about two weeks. He also had a persistent fever and severe diarrhea. There were hundreds of tiny blisters covering his body. Finally, a biopsy was done and, three days later, the patient was diagnosed with SJS/TEN.</p> <p>Patient died _____</p>
7	ISR#5206823 US 016856	2006	17 F SJS	<p>A 17 year old female who was taking multiple medications, including lamotrigine as part of a clinical trial, developed SJS requiring hospitalization on day 42 of modafinil 300 mg daily therapy. One month later she received modafinil 50 mgs and within 3 hours developed a rash. The rash, however, was milder than before. Skin biopsy was not available. Additional information from this patient was submitted 2/13/07. She had not been rechallenged with lamotrigine. He was not taking anti-epileptic medications.</p>
8	ISR#5194832 US 019026	2006	49 F SJS/TEN/ EMM	<p>Initially reported by a physician via sales representative on 12/12/06. A 49 year old woman with history of SLE, on multiple medications including prednisone, azathioprine, celecoxib, duloxetine, propranolol, chlorazepate, melizine, nystatin, fentanyl patch and medical marijuana. She also had a history of allergy to penicillin (hives), sulfa (dizziness) and hydroxychloroquine (pruritus). On _____ she underwent surgery for lumbar stenosis and received preoperative cefazolin (2 g IV x1). On 11/3/06 she initiated Provigil 200 mg/day. On _____ she developed rash, dysphagia and rigors. She was treated with IV hydrocortisone and oral fluconazole (for oral thrush) and transferred to another hospital. Blood, cerebrospinal fluid and urine cultures were negative. Throat culture grew beta streptococcus (not group A) and Candida albicans. The rash that started as a papular rash on the face and upper neck progressed and evolved to blisters, spreading to 50% of her body, including the oral and conjunctival mucosa. The initial reporter considered the event to be likely related as Provigil as it was the only new medication added to the patient's medical regimen. Provigil was stopped on 11/27/06. On 11/30/06 she was admitted to a burn unit with diagnosis of SJS/TEN and was treated with IVIG and antibiotics. Except celecoxib all medications were continued during hospitalization. The patient is recovering. Pictures are consistent with SJS/TEN. A punch biopsy from 11/29/06 was reported as Erythema Multiforme Major and was positive for staphylococcus aureus.</p>

b(6)

9	ISR# 5013599 US016978	2006	31 F	Rash eosinophilic myocarditis (Death) ?multi-organ hypersensiti vity	<p>This case described the occurrence of giant cell myocarditis in a 31-year-old female patient. On 04 February 2006, the patient started Modafinil (Provigil) for multiple sclerosis fatigue. Concurrent medications included oxcarbazepine, sertraline and topiramate. On 07 February 2006, the patient experienced erythema around both eyes followed by a raised, itchy rash involving the face and scalp, followed by profound discharge from both eyes and vaginal itching. At the urgent care center, the patient was given a prescription for an antihistamine. The prescription was miss-filled with generic Chlorpromazine HCl. The <i>erythematous rash</i> worsened and on 10 February 2006, advanced further to the jaw line. On 25 February 2006, the patient had a fever of 101 degrees F, and her blood pressure dropped to 70/50 mmHg. Total white blood cell count was 11,000 (units not provided), 7% eosinophils and 720 actual eosinophils (reported as 0.72), sedimentation rate 10. Despite supportive measures, the patient's condition deteriorated and on _____, the patient died. Initially, the reporting physician considered the events were possibly related to treatment with Chlorpromazine hydrochloride and likely related to Provigil. Upon follow-up, the physician stated the events were unlikely related to Provigil, and more likely related to an undefined autoimmune disorder. The autopsy cause of death was giant cell myocarditis with a differential diagnosis of eosinophilic myocarditis.</p>
10	ISR#? US 017511	2006	46 F	Multi-organ hypersensiti vity	<p>46 year old female developed a diffuse maculopapular skin rash, and fever, originally reported as SJS by a psychiatrist, on day 8 of modafinil treatment. She was taking concomitant lamotrigine, which was immediately discontinued, but the rash worsened and she developed elevated liver enzymes. Eventually, modafinil was discontinued and she had a positive rechallenge twice within one hour of modafinil re-initiation, but it was a milder skin rash, and the biopsy was read as interstitial granulomatous dermatitis.</p>
11	ISR/#5060040 US 017698	2006	15 M	Drug hypersensiti vity DRESS	<p>A 15 year old male who was otherwise healthy initiated on 4/13/06 Provigil with increasing doses up to 400 mg daily for the treatment of ADHD. Five weeks later, the patient presented with limb extremity rash that progressed to generalized body rash with fever (38 degree C). In the ensuing days, the patient developed fatigue, myalgia, vomiting, rhinorrhea, and dry cough. He was treated with ibuprofen. Subsequently, the patient was hospitalized and all medications including Luvox, Zyprexa, and Abilify that were prescribed since 2005 and Provigil were discontinued. On admission, he had fever, fatigue, and generalized maculo-papular rash with no mucous membrane involvement. Petechiae was observed on the soft palate and there was noted facial edema. He was tachycardic, with a questionable murmur, but hemodynamically stable. Admission blood laboratory values revealed 37% eosinophils, 25,000 WBC's, and BUN/ creatinine levels suggesting a pre-renal state. A dermatologist diagnosed it a drug reaction with eosinophilia and systemic symptoms (DRESS), subsequent to a skin biopsy (site unspecified) which showed eosinophilia and unspecified findings consistent with drug hypersensitivity syndrome. Within 24 hours of admission, the patient showed signs of coagulopathy. The Palmar petechiae were observed, and the patient was unable to eat, his face, hands, and feet were markedly edematous, and he continued to experience intermittent pyrexia. Meanwhile, blood titers were negative for IgM, measles, and Rubella. All viral and bacteria cultures were negative. In a short time,</p>

				the patient's vital signs became unstable with bradycardia, hypotension. A chest x-ray revealed bilateral, fluffy alveolar opacities and alveolar edema. The patient was transferred to the intensive care unit where he was placed on mechanical ventilation. The patient was supported with dopamine for blood pressure support and steroids and intravenous immunoglobulin therapy. The patient went on to develop pancreatitis and hepatitis as the pancreatic enzymes and liver transaminase levels were markedly elevated. Labs (amylase 542 (n=40-220), lipase 788 (n=7-60), AST 240 (n=2-40), and ALT 186 (n=3-30). The patient remained hemodynamically stable and the patient was extubated on 6/2/06. Coagulopathy had resolved (INR 1.09, PTT 27.2), the eosinophil count was 1%, and the WBC count was 5.7. All viral and bacteria cultures remained negative. Desquamation of the rash continued but was showing signs of recovery.	
	US 009180	?	61 M	? multiorgan hypersensitivity	History of Parkinson's disease, HTN and hepatitis C. He began modafinil 400 mg/day for daytime somnolence. Two days later he developed fever, nausea, weakness, sweating and decreased appetite. Modafinil was d/c. Two days later, with symptoms unchanged, he restarted modafinil. Eight days later, and ID specialist discontinued modafinil. Pt was hospitalized to determine the cause of his "fever, hyper BR and decreased blood cell and platelet counts. He had splenomegaly, cholecystitis, cholestatic hepatitis and sepsis. During exploratory laparotomy, he had a cardiac arrest and died. The final diagnosis was "Lymphoproliferative disorder". <i>This could be an explanation for the clinical presentation, but the narrative does not provide bases for the diagnosis of a lymphoproliferative disorder.</i>
	US 013895064	?	26 F	? multiorgan hypersensitivity	Patient developed low-grade fever, chills, headache, body aches, nausea, vomiting, dizziness, confusion and hyperventilation" after 3 months of modafinil treatment. She was also taking lamotrigine. She was hospitalized with a presumptive diagnosis of bacterial meningitis. No organism was identified in blood or CSF cultures. She developed a petechial rash while in the hospital. After discharge, she took modafinil 200 mg and within the next 20 minutes developed "body pains, vomiting, fever and sensitivity to light"
	US 016358	?	41 F	? multiorgan hypersensitivity	A patient with history of pituitary adenoma began taking modafinil 200mg daily. Two days later she developed a fever (106 F). On day 5 (when modafinil was discontinued) she developed petechial oropharyngeal rash with thrombocytopenia, leukopenia and hypotension. Her ANA titer was >1:640 and ESR was 57, leading to the diagnosis of SLE
	US 010763	2006	22 F	? multiorgan hypersensitivity	The patient initiated modafinil 200 mg/d on 2/27/03. After the second dose she experienced a severe allergic reaction consisting of hives that began on her ears and then covered her body, with neck swelling, lymphadenopathy, joint pain and fatigue. She was treated with Benadryl and oral corticosteroids and an unspecified injection. Modafinil was discontinued on 2/28/03. Labs are not available. The patient improved. This postmarketing case was reported by a nurse on 6/23/06.
	US 012767	?	38 M	? multiorgan hypersensitivity	Patient had a history of HIV+ and TB. On Day 11 of modafinil treatment was hospitalized for back/thank pain, fever, chills and rash on trunk and face, transaminases. Events resolved within 7 days.

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