

MEMORANDUM

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

DATE: October 12, 2005

FROM: Paul J. Andreason, M.D.
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Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation of Approvable Action for Supplement 019 Modafinil for the Treatment of ADHD.

TO: File NDA 20-717 Supplement 019
[Note: This memo should be filed with the original December 20, 2004 submission of this NDA.]

1.0 BACKGROUND

Modafinil is currently marketed under the trade name PROVIGIL and it is approved in dosage strengths of 100 and 200-mg for the treatment of adults with excessive daytime sleepiness (EDS) associated with Narcolepsy, Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS), and Shift Work Sleep Disorder (SWSD). Modafinil is currently used off-label by some clinicians for the treatment of Attention Deficit Hyperactive Disorder (ADHD) in the US in children and adults based on limited but positive support from the literature (Taylor and Russo 2000; Rugino and Samscock 2003); it was also approved for the treatment of ADHD in Mexico in 2001.

Cephalon seeks approval of a second proprietary name; ATTENACE was not approved and another name is under review by DMETS.

The sponsor submits this supplemental NDA for the added claim of the treatment ADHD of in children age 6-17. It contains efficacy data from 3 pivotal trials and supporting data from phase 2 and pre-clinical juvenile animal studies. Juvenile animal studies explore the toxicity of the sulphone metabolite that has been measured at six-fold higher levels in children than in adults and adolescents.

The primary medical review in the Division Psychiatry products was performed by Glenn Mannheim, MD. The primary preclinical Pharmacology-Toxicology Reviewer is Aisar Atrachi, PhD. The primary Statistical Reviewer was Tristan Massie, PhD.

2.0 CHEMISTRY

The sponsor submitted Chemistry data in support of new 85, 170, 225, 340, and 425-mg dosage formulations. The drug substance has not changed. The CMC final review is pending at this date.

3.0 PHARMACOLOGY

The final pre-clinical Pharmacology/Toxicology review is pending at this date.

4.0 BIOPHARMACEUTICS

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-1) reviewed NDA 20-717 for modafinil film-coated tablets. A biowaiver for the 170, 255, and 340 mg tablets was granted. They found that this NDA supplement was acceptable provided that an agreement can be reached between the sponsor and the Agency regarding the language in the package insert, as well as the phase IV commitment regarding the dissolution method.

By way of recommendation OCPB stated that in addition to assessing the potential to induce CYP2C9 and CYP2C19, the potential to induce CYP2C8 should also be evaluated.

5.0 CLINICAL DATA

5.1 Efficacy Data

The FDA primary reviewers for the sponsor's pivotal efficacy data were the primary medical officer, Glenn Mannheim, MD, and primary statistical reviewer Tristan Massie, PhD. The sponsor presented results of three pivotal trials, all of which were positive on face; they are designated as studies 309, 310, and 311. Studies 309 and 311 were identically designed flexible-dosage studies with 9-week double-blind treatment periods. Dose ranges for studies 309 and 311 were from 170-425-mg. Both Drs. Massie and Mannheim concur that the three studies are significantly positive and I also agree with their conclusions.

Study 310 had a fixed-dosage design with a 7-week double-blind treatment period followed by a 2-week randomized-withdrawal period. There were two fixed doses based on weight in study 310-340-mg/day for patients weighing less than 30-kg and 425-mg for patients weighing greater or equal to 30-kg.. The following table from Dr Massie's review outlines the three studies' major characteristics:

STUDY #	RANDOMIZED N	RANDOMIZATION/ DOSING	DURATION	PRIMARY EFFICACY	AGES	COMPLETE N (%)
309	133 Modafinil 67 Placebo	2:1 Mod/Pla flexible dose: 170 to 425 mg/day	9 weeks DB treatment	ADHD-RS-IV (School Version)	6-16	100 (75) 41 (61)
310	126 Modafinil 64 Placebo	2:1 Mod/Pla fixed dose: 340 mg if weight < 30 kg 425 mg if weight ≥30 kg	7 weeks DB treatment then 2 week withdrawal period	ADHD-RS-IV (School Version)	6-17	7 weeks 80 (63) 40 (63)
311	164 Modafinil 84 Placebo	2:1 Mod/Pla flexible dose: 170 to 425 mg/day	9 weeks DB treatment	ADHD-RS-IV (School Version)	6-17	97 (59) 33 (39)

In all three studies, the primary measure of efficacy was the teacher/physician-completed ADHD Rating Scale, Fourth Edition (ADHD-RS-IV, School Version). Patients who completed at least 4 weeks of the double-blind treatment period and did not withdraw due to an adverse event were eligible to enroll in a 1 year open label extension study. All three studies were performed in North America.

There were no pre-designated key secondary endpoints in the statistical analysis according to Dr. Massie.

A total of 638 patients were randomized 2:1 in the three studies for a distribution of 423 in the modafinil treatment groups and 215 in the placebo groups. All three studies were positive for their primary endpoints (p<0.001). The treatment effect sizes observed in these studies are similar to those seen in studies of stimulant drugs in the treatment of ADHD. Tabular results from the three studies are as follows:

Study 309: Comparison of ITT-LOCF and Observed Case Results for ADHD-RS-IV (school)							
		PROVIGIL		PLACEBO			
Population	Study	N	LS Mean Change	N	LS Mean Change	LS Mean Difference	P- value*
ITT-LOCF	309	128	-17.5	66	-9.7	7.7	<0.001
OC	309	100	-19.9	41	-11.6	8.3	0.001

Study 310: Comparison of ITT-LOCF and Observed Case Results for ADHD-RS-IV (school)							
		PROVIGIL		PLACEBO			
Population	Study	N	LS Mean Change	N	LS Mean Change	LS Mean Difference	P-value *
ITT-LOCF	310	119	-17.2	63	-8.2	9.0	<0.001
OC	310	79	-20.2	36	-11.6	8.6	0.001

Study 311: Comparison of ITT-LOCF and Observed Case Results for Change in ADHD-RS-IV (School)							
		PROVIGIL		PLACEBO			
Population	Study	N	LS Mean Change	N	LS Mean Change	LS Mean Difference	P-value*
ITT-LOCF	311	163	-15.0	81	-7.3	7.7	<0.001
OC	311	97	-18.2	33	-10.7	7.5	0.032

* based on ANCOVA model adjusted for baseline ADHDRS Total, site, treatment (Dr. Massie's results)

Ages ranged between 6 and 17 years across the three pivotal studies and the mean age was 10. About 67% of patients were under age 12. Dr Massie therefore analyzed the age groups of 6-12 and 13-17 years. He found significantly positive results for the treatment group comparisons of the change in ADHD-RS-IV total score (school version) in both age subgroups in studies 309 and 310. There were 61, 58, and 90 patients age 12 or older in studies 309, 310, and 311, respectively. In study 311 the treatment comparison was only significant in the age < 12 subgroup but overall there is no real evidence of a difference in efficacy between the age subgroups.

5.2 Safety

This will potentially represent the first approval of modafinil for the treatment of children in the US. There were no deaths in the controlled trials submitted with this supplement.

Adverse Events of Note

Serious Skin Reaction-Stevens Johnson Syndrome

Markham Luke, MD provided expert dermatological consultation for selected cases of severe skin reaction and Stevens-Johnson syndrome. He agreed that the case identified as Stevens-Johnson syndrome was appropriately classified. He stated that the case may be due to Amoxicillin allergy and recommended that the patient be tested for penicillin allergy as well as sulfone sensitivity. The hospitalized patient may likely have a skin biopsy available and this should also be considered. Dr. Luke suggested that more specific evaluations regarding drug rashes might be requested in future studies with modafinil. Drug rashes should be assessed by a qualified dermatologist. Skin biopsy where appropriate should be obtained. Photographs for documentation are encouraged. I agree.

Dr Mannheim believes that there is an increased risk of serious skin reactions in children associated with modafinil use. This conclusion is based on the one case of Stevens-Johnson syndrome and two other cases of serious skin reactions. I tend to agree that there appears to be an increased risk for serious skin reactions in the modafinil treated children in the absence of any clarifying data. Stevens-Johnson syndrome rarely occurs in the context of controlled clinical trials. It is quite rare and is often considered drug-related when it does.

The following are summaries of the cases of skin rash that were reported in this submission. There was one serious case of skin rash that was diagnosed as Stevens Johnson syndrome in the double blind placebo controlled patient pool. In study 311 Patient 062338- experienced extensive skin peeling with mild to moderate skin blistering. On study day 22, the pediatrician noted the rash had spread to the patient's face. On study day 23, the patient complained of burning with urination, which was considered the onset of mild Stevens-Johnson syndrome, with 2 areas of mucosal involvement, the urethral meatus and the upper and lower lips. A dermatologist assessed the patient's rash as erythema multiforme by history and most likely Stevens-Johnson syndrome by definition.

Along with this there were two other cases of serious rash in the phase 2 trials, one requiring hospitalization and the other antibiotics and acetaminophen with codeine for pain management. In study 207, Patient 315-was hospitalized for rash but it was ultimately not considered as Stevens Johnson syndrome by the dermatologist. In study 213, Patient 18004 developed a vesiculobullous - "moderate rash" with "severe blisters on lips". Cephalaxin was given for this blistering rash and acetaminophen with codeine was given to treat the fever and pain related to the rash. It appears that this patient was treated as an out-patient. None of these patients were re-challenged with modafinil.

Dr Mannheim's review also suggested that there is a potential increased risk for skin sensitivity reactions because of a high rate of insomnia associated with modafinil. He reasoned that insomnia associated with modafinil treatment might be treated with a drug that might lead to potential, but as yet unknown drug interaction that could increase the risk of skin sensitization. In a personal discussion with Dr. Mannheim on this issue, he stated that this was a hypothetical concern and he did not have any particular drug interaction in mind.

There is an example of a specific drug interaction between Lamictal and valproate in children with seizure disorder that appears to increase the risk of a serious skin reaction. Generally there is a higher risk of serious skin reactions with Lamictal treatment. Children treated with Lamictal have a higher risk for developing serious skin reactions (Stevens-Johnson or Toxic Epidermal Necrolysis) than adults. Additionally, a link has been made between valproate use with Lamictal as an increased risk for serious skin reactions, but there are no other drug interactions that increase this risk to my knowledge.

Generally speaking, gratuitous poly-pharmacy is avoided in the practice of medicine. That said, to my knowledge there is no specific added hesitation to co-prescribing sleep or other drug products besides valproate with Lamictal for fear of increasing the risk of serious skin reactions. I therefore do not see that an additional general warning against co-prescribing with modafinil would be indicated until there was evidence to support such a precaution.

Elevated Transaminases

There were three cases of markedly elevated liver enzymes. Summary information is included below:

Patient 056003, was a 9-year-old white boy with a diagnosis of ADHD, who began treatment in the open-label study with 85 mg/day of modafinil on 25 February 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 311. He had a prior history of insomnia, allergy to Septra, and otitis media. He was taking multivitamins at entry into the open-label study. On study day 13, the patient experienced moderate fever, general body hives and swollen eyes (COSTART: facial edema) and mild vomiting; these events were considered by the investigator to be probably related to treatment with study drug and resulted in withdrawal of the patient from the study on study day 14. His last dose of study drug was on study day 13. The patient was treated with paracetamol for fever, and the fever and vomiting resolved with no residual effect on study day 13. The patient also was treated with Benadryl for urticaria and facial edema, which resolved with no residual effect on study day 23. In addition, on study day 14, the patient had a severe elevation of alanine aminotransferase (ALT) 517 U/L, normal range 5 to 30 U/L and a severe elevation of aspartate aminotransferase (AST) 409 U/L, normal range 0 to 41 U/L. These events were considered probably related to treatment with study drug by the investigator. SGOT increased and SGPT increased resolved on study day 23 and study day 35, respectively, with no residual effect. The final values available for SGOT and SGPT were 29 U/L and 28 U/L, respectively, on study day 48. The patient began treatment with atomoxetine hydrochloride for ADHD on study day 25, 12 days after the last dose of modafinil. I do not have bilirubin values for this patient. If the bilirubin is elevated to >2X ULN then one could consider this a case of serious liver injury.

A patient in study 311, 63329, a 17 year old black male, has no clinical summary that I could find included in the submission but had a reported ALT of 453 u/l(>10X ULN) AST of 269 u/l (9X ULN) in open label.

A patient in study 309, 006120, was a 9 year-old white male, who experienced an AST >8X ULN (262 u/l). I was not able to locate a summary for this patient or adverse events associated with the timing of this patient's elevated labs.

Regarding other measures of potential drug-induced liver toxicity, there was no mean increase in serum transaminase values and there was not a disproportionate number of patients with potentially clinically significant (PCS) elevations in their laboratory values (see table below).

**Clinically Significant Serum Chemistry Values by Treatment Group Phase 3
Double-Blind, Placebo-Controlled Studies, and All Studies Combined**
Number (%) of patients

Serum chemistry variable	Criteria	Phase 3 double-blind, placebo-controlled studies		All studies combined
		Modafinil (N=420)	Placebo (N=213)	Modafinil (N=933)
Uric acid	M: ≥ 625 $\mu\text{mol/L}$ F: ≥ 506 $\mu\text{mol/L}$	0	0	1 (<1)
AST	≥ 3 x ULN	0	0	3 (<1)
ALT	≥ 3 x ULN	3 (<1)	1 (<1)	8 (<1)
Alkaline phosphatase	≥ 2 x ULN	0	0	5 (<1)
GGT	≥ 3 x ULN	1 (<1)	0	5 (<1)
Total bilirubin	≥ 34.2 $\mu\text{mol/L}$	0	0	1 (<1)

SOURCE: Summaries 5.5.1 and 5.5.3.

male; F=female; ULN=upper limit of normal range; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transpeptidase.

Reye Syndrome

The Division consulted John Senior, MD of the Office of Drug Safety (ODS) on this case of what appeared to be Reye syndrome. This case occurred in a study of modafinil in the treatment of excessive sleepiness associated with narcolepsy. This came to Dr. Mannheim's attention as IND Safety Report: US014983 late in the review cycle. The listed adverse events associated with this case were Delirium, Seizures, Increased Serum Ammonia, Decreased Serum Phosphate, and Confusion. Dr Mannheim grouped this case with the cases of elevated transaminase (because Reye-like syndrome does often include increased serum transaminases); however, according to Dr Senior in a personal discussion of the consult, there is no mechanistic similarity to idiosyncratic hepatocellular injury that is associated with drug toxicity and Reye Syndrome, a mitochondrial disorder. In this particular case, there was no documented increase in serum transaminases, though in Reye syndrome this may occur. Dr Senior states that in Reye syndrome, when transaminases rise they do so without a concomitant rise in bilirubin. The Division asked the Cephalon to follow up on this case; however, they stated that the patient's family had declined to give consent for Cephalon to have copies of the hospital records. Dr Senior notes that there is no history of this patient receiving aspirin. Dr. Senior does not conclude that this case is drug-related or related to the other isolated cases of liver transaminase elevation seen in this submission.

Leukopenia

The Division had been concerned about a signal for leukopenia associated with the use of modafinil. A consult was obtained from ODS to review reported cases of leukopenia. That consult was also summarized in Dr. Mannheim's review. There were no reported pediatric cases of leukopenia in the post marketing adverse event database. There was no signal for increased risk of leukopenia in children in the controlled trial database.

Psychiatric Adverse Events

Dr Mannheim notes that 52 modafinil patients and 8 placebo patients discontinued prematurely due to adverse events. He notes that psychiatric adverse events of suicidality, depression, agitation, psychosis and phobias were only reasons for dropout in modafinil treated patients. Placebo treated patients dropped out largely for reasons of lack of efficacy.

ADHD is often a co-morbid condition with other psychiatric disorders. For this reason, psychiatric adverse events are commonly reported in association with drug treatment. It is not reasonable to assign causality of such an event to a drug treatment merely because it had a temporal relationship with it. This is because these psychiatric adverse events also often occur even in the absence of drug. It is nearly impossible to assign causality to open-label or post-marketing reports of commonly occurring serious events that occur as part of co-morbid conditions or the illness itself. For this reason, the Division in collaboration with ODS recently sent letters to all sponsors of drugs used to treat ADHD requesting that they examine their controlled trial databases for specific psychiatric adverse events that occurred during controlled clinical trials. The controlled trial databases will be analyzed to see if there is a difference in the relative risk for these events with treatment. The letter requesting this information and analysis was sent to Cephalon on September 15, 2005. As part of a complete response to this action letter, I recommend that Cephalon adequately respond to the Division's letter of September 15, 2005.

5.3 Clinical Sections of Labeling

In the **CLINICAL TRIALS** section of draft labeling there are statements that celebrate treatment effects for both the hyperactive and inattentive symptoms. I believe that these distinctions in the sub-symptoms of ADHD should be excluded from the **CLINICAL TRIALS** section because they are pseudo-specific in nature and imply a false advantage. The diagnosis of ADHD already encompasses both hyperactive and inattentive symptoms. The Division has not allowed key secondary variables in labeling that are subsets of the primary efficacy rating variable.

A display of the pooled data and description of teacher, parent and physician scales is likewise not appropriate in my opinion. Analysis of pooled data and parent and physician scale scores were not the primary efficacy variables and do not represent significantly different treatment domains to be mentioned in labeling as key secondary variables.

I believe that the **INDICATIONS** section of labeling is acceptable.

If the requested exploration and analysis of suicide related adverse events exhibits an increased risk for these events with modafinil, then a black-boxed warning, similar to the recently requested labeling for Strattera seems appropriate.

I recommend that the **WARNINGS** section of labeling include at least a bolded warning for the case of Stevens-Johnson syndrome. I believe that the sponsor should submit this as CBE labeling prior to a final action for the ADHD indication. A question for PDAC could be if this is appropriately strong labeling whether approved for ADHD or not.

The **PRECAUTIONS- Central Nervous System** discusses psychosis. It implies that there have only been two observed cases. This section should be revised and updated. Dr Mannheim's review refers to at least three adverse dropouts for psychosis who had no previous history in this development program.

The *Cardiovascular System* section already implies that patients with structural cardiac defects should not receive modafinil. We may wish to add this particular language to the labeling as it was done with Adderall XR.

In the ADVERSE EVENT section *Insomnia and Anorexia (decreased appetite)* draft labeling suggests that the adverse events of insomnia and anorexia decrease with continued use. This claim is based on a decrease in spontaneous adverse event reporting. These studies were not designed to illicit or temporally monitor these adverse events. Once these events are reported they may be continuing but not reported. I believe that a decrease in spontaneous reporting rates over time, though suggestive habituation, is not proof of decreasing adverse drug experience over time and should not be suggested at this point in product labeling.

6.0 WORLD LITERATURE

There were no literature reports for severe liver toxicity, Reye syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, or serious skin reactions associated with modafinil treatment in a MEDLINE search that I performed on October 3, 2005. This was also confirmed by Dr. Luke's search.

7.0 FOREIGN REGULATORY ACTIONS

Modafinil, under the brand name Modiodal, was first approved in France in 1992 for the treatment of narcolepsy, with or without cataplexy, and idiopathic hypersomnia. Modafinil is currently marketed in 27 countries for one or more of 6 indications relating to narcolepsy or other sleep disorders.

Modafinil is currently approved for the treatment of ADHD in Mexico only. It was approved for this use on November 1, 2001 and is also marketed under the same brand name Modiodal®, by Armstrong Laboratories. It is approved for use in ADHD patients 5 years of age and above, up to a maximum dose of 400 mg/day. Modafinil has not been withdrawn from marketing for any reason related to safety or effectiveness. Approval for ADHD is not pending in any other country.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We did not take this supplement to the PDAC on this review cycle; however, given the case of Stevens-Johnson syndrome and two other cases of serious skin reaction I recommend that the Division present this supplement to the PDAC as part of the review of their complete response to this upcoming action.

9.0 DSI INSPECTIONS

Three clinical sites were inspected by the Division of Scientific Investigations (DSI): Drs. Ball, Knutson, and Boellner's sites enrolled a large number of subjects in the U.S. for protocols 311, 310 and 309, respectively. The goals of inspection included validation of submitted data and compliance of study activities with federal regulations and good clinical practices. The data appeared to be acceptable from all of these sites.

10.0 CONCLUSIONS AND RECOMMENDATIONS

The data presented in trials 309, 310, and 311 are convincing that Modafinil is effective in the treatment of ADHD in children and adolescents. I recommend that the Division take an Approvable Action on this supplement as opposed to a Not Approved Action as Dr. Mannheim suggests. I differ in my recommendation because I feel that I need more information before passing final judgment on the acceptability of using modafinil in the pediatric ADHD population. I do not at this point see that further studies need to be performed to establish efficacy; however, more safety information

concerning the patients that have already been studied would be very helpful. I agree with Dr Markham that penicillin and sulfone sensitivity testing could be helpful on the patient with Stevens Johnson syndrome as well as sulfone sensitivity testing on the other two patients with severe skin reactions.

The case of Stevens-Johnson syndrome concerns me from the view-point of safety. Dr. Mannheim recommends a Not Approved action based on the cases of serious skin reaction in concert with other more common and less serious adverse events such as a high rate of insomnia and other psychiatric adverse events. I believe that the serious skin reactions must be considered separately from insomnia and other adverse events since many useful drugs have these types of adverse events associated with their use.

I recommend that the one identified case as well as the two other serious skin reaction cases need to be further explained and their descriptions potentially placed in draft labeling by the sponsor. I believe that we should bring the concern about a potential increased risk for serious skin reactions to an advisory committee. None of these three cases resulted in death. Based on the information that we have, none of the three were treated in the ICU or burn unit. Black-box warnings have usually been reserved for adverse events that have resulted in death or organ transplant (as in cases of liver failure). I would therefore recommend at least a bolded warning in draft labeling based on these cases.

The rates of insomnia though high, but are not in the majority and are not significantly different from amphetamine. Psychiatric adverse events in association with the treatment of psychiatric conditions with psychotropic drugs are commonly occurring events. These events occur with other ADHD treatments, do not occur with most patients, may be monitored clinically and are self limited. Nonetheless, I believe that the psychiatric adverse event profile of modafinil needs better characterization and description before I would recommend approving this application. This will be accomplished by Cephalon responding to the Division's September 15, 2005 request letter.

The Agency has searched for cases of leukopenia in the post-marketing adverse event reports database. There are no cases of leukopenia reported in children. I therefore do not believe that leukopenia is of any greater concern in the pediatric population treated with modafinil based on the data that I have at this time. ODS, as always, will continue to monitor this. I do not believe that the sponsor needs to present any more information on the current leukopenia data, but they, like ODS should continue to monitor this and report this adverse event when it occurs.

I concur with Dr. Senior that the Reye syndrome case can not be causally linked to modafinil treatment.

There were three cases of markedly elevated liver transaminases associated with modafinil treatment. None of these cases resulted in death, liver transplant or jaundice. There was no mean difference in the serum transaminase values and there were no treatment group differences in the number patients with PCS elevations in transaminases in the controlled trial database. Nonetheless, I would like more complete information on these three patients that I identified in this memo (Patient 056003; study 311, 63329; study 309, 006120) to further evaluate the potential role of modafinil in these events.

I generally recommend against second proprietary names. We have recommended against multiple proprietary names in the past at the Division level based on concerns about double prescribing and name confusion (e.g. Wellbutrin and Zyban), but have been routinely over-ruled at levels above the

Division. Mexico markets modafinil under the same name for ADHD as for narcolepsy. Since Provigil is already used for ADHD off-label and non-psychiatrists would start prescribing modafinil more often after approval, then it is conceivable that modafinil under another name could be prescribed on top of an already existing Provigil prescription. 825-mg of modafinil would be the maximum combined recommended dose in such a scenario. We do not have enough data to reliably predict the outcome of an 825-mg dose in any one individual or group. There has been only one accidental overdose of 800-1000-mg in a child thus far. The symptoms in the child were reportedly non-serious and they recovered. I doubt that 825-mg overdoses would result in uniformly serious outcomes, but I also doubt that they would be asymptomatic. A second proprietary name for modafinil should present no greater risk for children than the existence of two different brands or formulations of amphetamine containing products on the market (e.g. Adderall and Dexedrine).

After considering the range of Cephalon's probable responses to this intermediate action, I believe that it seems reasonable to consider two options for a future final action. The Division could either approve modafinil for treating ADHD with adequate labeling, or not approve it based on this perceived increased risk of serious skin reactions. Because either decision seems ultimately reasonable, but at the same time controversial, I would like to bring this question to the PDAC.

Rugino, T. A. and T. C. Samscock (2003). "Modafinil in children with attention-deficit hyperactivity disorder." Pediatr Neurol **29**(2): 136-42.

Taylor, F. B. and J. Russo (2000). "Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults." J Child Adolesc Psychopharmacol **10**(4): 311-20.

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