MEMORANDUM

DATE: September 21, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 20-717/SE-021

SU BJECT: Action Memo for NDA 20-717/SE-021, for the use of Provigil (modafinil) Tablets in the treatment of pediatric patients with narcolepsy

NDA 20-717/SE-021, for the use of Provigil (modafinil) Tablets in the treatment of pediatric patients with narcolepsy, was submitted by Cephalon on 12/21/05. The application contains the results of a single randomized controlled trial (Study 3027) in pediatric patients, as well as safety information and pharmacokinetic data in this population. The application has been reviewed by Dr. Elizabeth McNeil, medical officer, Dr. Sharon Yan, statistician, Dr. Atul Bhattaram, Office of Clinical Pharmacology, Dr. Nallaperumal Chidambaram, chemist, and Dr. Khairy Malek, Division of Clinical Investigations. Both Drs. McNeil and Yan find that the single study does not provide substantial evidence of effectiveness of modafinil as a treatment for pediatric patients with narcolepsy, although Dr. McNeil recommends that the sponsor be sent an Approvable letter. I will briefly review the major findings, and offer the rationale for the division's action.

As both Drs. McNeil and Yan note, this supplement was submitted in response to a Written Request issued (WR) by the Agency. The original request asked for a study in Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) as well as a study in narcolepsy. The sponsor initiated a study in OSAHS, but found recruitment too difficult and slow. As a result, the Agency issued an amended WR in which we asked for a controlled study only in patients with narcolepsy. In addition, we requested pharmacokinetic and safety data.

EFFECTIVENESS

Study 3027

This was a randomized double blind multi-center study in which patients aged 5-17 years with narcolepsy were randomized to received either modafinil 100 mg, 200 mg, or 400 mg/day or placebo for 6 weeks. There were two co-primary outcomes: 1) Change from Baseline to Final visit in the mean Multiple Sleep Latency Test (MSLT), and 2) the proportion of patients with improvement on a 7-point Clinical Global Impression of Change (CGI-C). The primary analysis of the MSLT outcome was to be a linear trend test.

A total of 166 patients were randomized at 46 centers in the US and Canada.

The following chart displays the results of the individual dose groups for the intent-to-treat population as typically defined (at least one dose and at least one rating):

MSLT	Pro 400 mg (N=36)	Pro 200 mg (N=40)	Pro 100 mg (N=40)	Pla (N=40)
Change	3.01	4.83	3.76	0.60
CGI-C				
% Improved	73%	83%	85%	66%

The p-value for the linear trend test for the MSLT was 0.06. The p-value for the combined Provigil groups with the protocol-specified chi square test for the CGI-C was 0.052.

Although the protocol did not specify a procedure to test for the effectiveness of the individual doses for the MSLT, Dr. Yan performed several such tests, including the Dunnett's adjustment and individual pairwise comparisons. The p-values for the Dunnett's test were 0.046, <0.001, and 0.005 for the 400, 200, and 100 mg doses, respectively. For the individual comparisons, the p-values were 0.024, 0.0001, and 0.003, respectively. As Dr. Yan points out, the 400 mg dose would be considered positive either with a stepdown procedure or a Hochberg procedure, but not with a strict Bonferroni correction.

Although the chi square test of the CGI-C reaches significance (for all intents and purposes), comparisons of the individual doses with placebo yielded the following p-values: 0.5, 0.08, and 0.04, for the 400, 200, and 100 mg doses, respectively, without correction for multiple comparisons.

SAFETY

As Dr. McNeil describes, the sponsor presented safety data from Study 3027, 3028, the aborted study in patients with OSAHS, Study 3029, an open-label extension of Studies 3027 and 3028, and Study 3034, a 6 month open label study. In total, the sponsor has submitted safety data in 270 patients with either narcolepsy or OSAHS. In addition, the sponsor referred to safety data recently submitted in a supplement in which the sponsor presented data from studies in pediatric patients with ADHD.

Dr. McNeil's Table 5, Page 41 of her review, displays a comparison of adverse events (AEs) in the Provigil and placebo groups in Study 3027. As can be seen in that table, there a few AEs that occurred more frequently in the drug-treated compared to the placebo-treated patients (for example, insomnia, rhinitis, pharyngitis, dysmenorrheal, abdominal pain, fever) but these typically occurred in

only a few patients and were not serious. For AEs that occurred in more than one patient, there was no clear evidence of dose response, but, as Dr. McNeil notes, the number of patients in the fixed dose study was relatively small.

There were no deaths, but Dr. McNeil describes numerous serious AEs (SAEs).

There were a total of 2 SAEs in Study 3027; a 6 year old boy who developed nausea, vomiting, and fever on Day 12 at a dose of 400 mg/day. He subsequently became somnolent and confused, and experienced seizures and delirium with hallucinations. He had a serum ammonia of 145. Other CNS work-up was negative. He was diagnosed with viral encephalitis, the symptoms of which resolved, with fever and somnolence persisting until Day 48. He was discontinued from treatment.

A 12 year old boy had appendicitis.

There were 2 SAEs in Study 3029; one suicide gesture, and one kidney infection. There was one SAE in Study 3034, a 12 year old boy who lost a few kilograms of weight over about 6 months (he also had a pre-existing osteofibroma resected on Day 8 of treatment).

Dr. McNeil provides narrative summaries of the patients who discontinued treatment from one of the four studies performed. There were few dropouts from AEs in the controlled studies, and several discontinuations in the open-label studies related to behavioral changes that were difficult to clearly ascribe to drug.

Dr. McNeil also describes numerous cases of psychiatric adverse events in open-label trials, including aggression, hostility, agitation, a number of which resolved with continued treatment. Many of these children had psychiatric histories. She also describes similar events seen in the ADHD trials, including several cases of suicidal ideation and gestures. It is difficult in this population (ADHD) to clearly ascribe these events to treatment with modafinil. In many of these cases, treatment with modafinil was continued.

Dr. McNeil also describes several cases of rash, although there seems to be no specific rash described.

Most importantly, a case of what appears to be Stevens Johnson syndrome occurred in a 7 year old boy who had been treated for 16 days. This case has been reviewed extensively by internal and external experts. Indeed, this case provided the basis of the Division of Psychiatry Products' recent Not Approvable letter to the sponsor. Although the drug was shown to be effective in ADHD, this single case prompted DPP to present the data to its Advisory Committee, who felt that the sponsor should expose at least 3000 more patients without another case of SJS to cap the risk of SJS at an acceptable incidence. The sponsor feels strongly that this is not, in fact, a case of SJS, [redacted]

There are no important clinical laboratory or vital sign changes.

COMMENTS

The sponsor has submitted the results of a single randomized controlled trial designed to support an indication for Provigil in the treatment of pediatric patients with narcolepsy.

The sponsor's protocol-specified primary analyses of the co-primary outcomes MSLT and CGI-C almost reached nominal significance; p=0.06 for the linear trend test of the MSLT and p=0.052 for the chi square test for the CGI-C. Although the trend test did not technically meet the prespecified level for significance, reasonable analyses of the individual doses do yield significant levels for all three doses, in my view, although clearly the 400 mg dose performs the worst, for reasons that are not clear.

However, despite the near significance for the chi square test for the CGI-C, analyses of the individual doses yield results that are difficult to interpret. Only the 100 mg vs placebo contrast reaches nominal significance, and would not be considered positive with any reasonable correction for multiple comparisons or a typical stepdown procedure. Although the lack of significance of any dose may simply be related to inadequate power for any of the single dose-placebo comparisons, the outcome of these pairwise analyses does not easily translate into meaningful dosing recommendations. Certainly, there is no evidence from this study that doses greater than 100 mg are more useful than 100 mg/day, but the analyses do not firmly establish the effectiveness of even this lowest dose (at least as measured by the CGI-C). For this reason, I do not believe that the sponsor has provided adequate data to support the effectiveness of any given studied dose of modafinil in pediatric patients with narcolepsy.

I do not believe that the sponsor has provided any safety data that would otherwise preclude approval of modafinil in this population. However, as noted above, the Agency still concludes that one case of SJS has occurred in a pediatric patient, and the current estimate of the incidence of SJS in the pediatric population was deemed unacceptably high to permit the drug's approval in ADHD. We do not have to directly address the question at this moment of whether or not this incidence of SJS would preclude the approval of modafinil for pediatric patients with narcolepsy (of course, the risk-benefit considerations are different for narcolepsy and ADHD; for one thing, there are many other approved treatments for patients with ADHD, while there are no approved treatments for pediatric patients with narcolepsy). However, this question will need to be dealt

with if the sponsor provides additional data (or arguments) that convince us that modafinil is effective for pediatric patients with narcolepsy.

Although I acknowledge that Dr. McNeil has recommended that the division issue an Approvable letter, I believe that the sponsor has to provide evidence of effectiveness from an additional controlled trial before this indication may be granted. Under these circumstances, I believe a Not Approvable letter is appropriate, and I will issue the attached letter, with appended proposed labeling.

Russell Katz, M.D.

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/s/

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MEDICAL OFFICER