CONCLUSIONS.

Modafinil, 2-[(diphenyl, ethyl)sulfinyl]-acetamide, is pharmacologically related to the stimulants d-amphetamine, methylphenidate, and cocaine. *In vivo* studies have demonstrated that Modafinil increases locomotor activity and promotes wakefulness. Like other CNS stimulants, *in vitro* studies have revealed that modafinil has some binding affinity for the dopamine uptake sites. Modafinil's affinity for the uptake site was approximately five-fold lower than cocaine's affinity and 16-fold lower than d-amphetamine.

Evaluation of modafinil's dependence in a preclinical self-administration study and clinical study has suggested that its dependence capacity is equivalent to that of CNS stimulants. Results from the self-administration study showed that modafinil possesses reinforcing properties (i.e., functions as a positive reinforcer) in primates. Modafinil maintained self-administration behavior in primates trained to self-administer cocaine. In the preclinical animal model (drug discrimination study) for evaluating a drug' subjective effects, modafinil elicited partial stimulant-like discriminative stimulus effects (i.e., subjective effects).

Human abuse liability evaluation indicated that modafinil may possess stimulant-like dependence producing properties. Modafinil was shown to have stimulant-like pharmacological effects in volunteers with a history of substance abuse.

RECOMMENDATION.

FDA Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) recommends that Modafinil be regulated under the Controlled Substances Act as a Schedule IV drug, at a minimum.

HFD-170, also, recommends the following as the proposed label for PROVIGIL®:

1. **DESCRIPTIONS:** Page 1, lines 1 amd 2: Recommend change to read [redacted]

2. **CLINICAL PHARMACOLOGY:** Page 1, Consider adding that [redacted]

3. Information summarized under **Clinical Pharmacology** is not the most relevant. It is as important to add information from the self-administration and drug discrimination studies as well. See scheduling document.

4. **AGE/GENDER DIFFERENCES:** More than pk differences (Females >>>Males). Metabolism in females is evidently less than in males.

5. ADVERSE REACTIONS:

ASSOCIATION WITH DISCONTINUATION OF TREATMENT: Should specify percent of individuals in trials were on concomitant MEDS and the type of MEDS (Page 15).

6. **Recommend revising DRUG ABUSE AND DEPENDENCE section (on Page 20) to read as follows:**

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

[redacted]

Abuse Potential and Dependence

[redacted]

7. Recommend deletion of **Withdrawal** section (Page 22), because subjects were on concomitant medications during withdrawal of modafinil.

8. Recommend deletion of **Clinical Dependence** section (Page 21), because the U.S. study (Jasinski, FSK Med Ctr., Johns Hopkins) demonstrated that modafinil at above therapeutic doses was recognized as amphetamine-like, was "liked", produced euphoria in post addict volunteers in a single dose study. Study was placebo controlled, and used methylphenidate as positive control. A significant gender difference was observed in which the stimulant-like response in females was more intense than observed in males.

9. Under **OVERDOSAGE** section (Page 22), should state that modafinil and modafinil acid exhibited linear pharmacokinetics over a dose range of 40-499 mg. Also, females (35%) appeared to excrete less modafinil acid in urine than males (51%).

/S/ [redacted] 12/23/97

Silvia N. Calderon, Ph.D.

/S/ [redacted] 12/17/97

Igor Cerny, Pharm.D.

[redacted] 12/23/97

Michael Klein, Ph.D.

APPEARS THIS WAY ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL SAFETY REVIEW OF NDA

Brand Name:	**Provigil**
Generic Name:	**Modafinil**
Sponsor:	**Cephalon**
Indication:	**Narcolepsy**
NDA Number:	**20-217**
Original Receipt Date:	**6/30/98**
Clinical Reviewer:	**Joel Freiman, MD**
Review Completed:	**12/15/98**

BACKGROUND

NDA 20-717 was submitted by Cephalon, Inc. on 12/30/96, for the use of modafinil as a treatment for patients with excessive daytime sleepiness associated with narcolepsy. An approvable letter was issued on 12/29/97 requesting additional clarification of labeling, safety, and other issues. The sponsor resubmitted NDA-717 on 6/30/98 with responses to most of the issues in the12/29/97 approvable letter. This review will address only the sponsor's response to the safety issues raised in the 12/29/97 approvable letter. A separate clinical review will address the sponsor's update of the integrated summary of safety.

The predominant safety issue raised in the approvable letter relates to the long term exposure to modafinil at a dose of 400 mg/day. This issue arose as a result of the sponsor's desire to suggest a maximal daily dose of 400 mg/day even though the data from two effectiveness trials do not demonstrate any consistent, increased benefit of 400 mg/day compared to 200 mg/day. In addition, the sponsor did not submit sufficiently detailed data regarding the long-term exposure to 400 mg/day given as a single daily dose to permit a statement in labeling about the long term safety of this dose.

For the purpose of this review the specific safety issue question as stated in the 12/29/97 approvable letter will be followed by this reviewer's summary of the sponsor's response then followed by the reviewer's comments to the sponsors response.

SAFETY ISSUES

1. You state that you cannot be certain that the numbers of patients in the dose/duration cells in your tables of foreign data represent separate discrete individuals, raising the question of the accuracy of your statements that 2305 subjects have been exposed to modafinil.

Before we can approve your application, we must have as complete and accurate an accounting of subjects/patients exposed to modafinil as possible, with accurate corresponding dose/duration data for this cohort. Your re-submission should address this issue clearly and completely. Our staff will be happy to discuss with you the way in which this data should be submitted.

SUMMARY OF SPONSORS RESPONSE

SOURCE: VOL. 1 OF 67 ATTACHMENT 2

NON-CEPHALON SPONSORED STUDIES

METHODS

The sponsor re-evaluated all non-Cephalon case report forms (CRFs) to identify the number of unique patients exposed to modafinil worldwide among the 81 non-Cephalon-sponsored foreign studies with CRFs.

Among the non-Cephalon-sponsored studies there was no uniform subject identification system across studies. To determine the number of unique, identifiable subjects among

modafinil exposures the CRFs were reviewed with respect to all available identification and demographic information collected within the individual studies. Unique subjects were determined by matches in identification and demographic information.

RESULTS

The sponsor identified 1704 modafinil exposures. Of these 1704 exposures 1375 represented unique subjects exposed in a single study, 123 unique subjects exposed in more than 1 study (252 exposures), and 7 unique subjects in "clusters" of subject exposures (15 exposures), for a total of 1505 unique identifiable subjects.

A "cluster" of subject exposures occurred when insufficient identifying information was available to conclusively determine whether modafinil exposure represented unique subjects each participating in a single study, unique subjects participating in more than one study or some combination of these two groups. Since each cluster contains at least one unique subject the sponsor considered them as 7 unique subjects for the purposes of total subject exposure.

In addition, there were 62 subject exposures with such inadequate identifying information that no statement can be made about the unique subjects contained in this group. Such highly indeterminate subject exposures were termed "linkers."

CEPHALON-SPONSORED STUDIES

METHODS

The sponsor did not have to make any assumptions to calculate the number of unique exposures in the Cephalon sponsored-studies.

RESULTS

The sponsor identified 760 unique modafinil-exposed subjects. Among the 760 unique subjects, 600 subjects were from the blinded studies and from open label studies. An additional 160 subjects, initially in the placebo group of the double blind studies subsequently were exposed to modafinil in the open-label extensions.

DOSING INFORMATION (CEPHALON-SPONSORED AND NON-CEPHALON-SPONSORED STUDIES)

For each unique modafinil exposed subject who participated in a foreign (non-Cephalon-sponsored trial), his or her exposures were condensed into one composite exposure, with a duration equal to the sum of the individual exposures. Average daily dose was calculated over the summed exposures. Total subject duration of exposure to modafinil and dose information for subjects in Cephalon and non-Cephalon-sponsored studies are summarized in the sponsors Vol. 1, Table 1, p. 47 (Attachment 1). Since exact duration of exposure and dose could not be made among exposures classified as either "clusters" or "linkers", these exposures are not included in Table 1.

SPONSORS CONCLUSIONS

The sponsor identified 1505 unique modafinil exposed subjects from 81 non-Cephalon – sponsored studies and 760 unique modafinil exposed subjects from Cephalon-sponsored studies, for a total of 2265 modafinil exposed subjects worldwide. A total of 737 subjects were exposed for more than 180 days and 477 were exposed for more than 365 days.

COMMENTS

The sponsor has conducted a reasonable re-evaluation of the non-Cephalon-sponsored and Cephalon-sponsored studies to identify the number of unique subject exposures to modafinil worldwide. The total number of unique exposures (2265) is similar to the number (2305) cited in the original NDA.

There are limitations to the sponsor's categorization of subject exposure by dose and duration, especially in the non-Cephalon sponsored foreign clinical trials. Condensation of exposure time and computation of average daily dosage in the non-Cephalon sponsored foreign clinical trials is subject to the limitations of averaging (a subject may have participated in two trials of equal length one at 200 mg/day and the other at 400 mg/day, thus this subject would be classified with an average daily dose of 300 mg/day).

APPEARS THIS WAY ON ORIGINAL

With respect to the evaluation of safety to long term modafinil exposure it must be kept in mind that subjects participating in more than one trial may not have had continuous exposure.

From the sponsor's Table 1, among participants in the Cephalon sponsored studies with an average daily dose of 375-424 mg/day, 31 subjects had duration of exposure of 180-364 days and 12 subjects had duration of exposure greater than or equal to 365 days. No subjects had exposure too greater than 425 mg/day of modafinil for greater than 28 days.

From the sponsor's Table 1, among participants in the foreign non-Cephalon sponsored studies with a average daily dose of 375-424 mg/day, 47 subjects had a duration of exposure of 180-364 days and 86 subjects had a duration of exposure greater than or equal to 365 days. Among subjects with an average daily dose greater than or equal to 425 mg/day, 4 subjects had duration of exposure of 180-364 days and 42 subjects had duration of exposure greater than or equal to 365 days.

Overall exposure to an average daily dose of modafinil greater than or equal to 375 mg/day is limited.

2. Please clearly present accurate duration (and corresponding safety experience) data for subjects who have received single daily doses of 400 mg or greater; this information is currently unobtainable from your submission. In addition, please present duration

and corresponding safety data separately for subjects who have received daily doses of 400 mg or greater as twice a day dosing; there may be some overlap in these 2 cohorts (single daily dose and twice a day dosing).

SUMMARY OF SPONSORS RESPONSE

SOURCE: VOLUME 1 OF 67 ATTACHMENT 3A

METHODS

The sponsor utilized databases from both Cephalon-sponsored (through a data cutoff of June 2, 1997) and non-Cephalon-sponsored clinical studies for which Cephalon had access to the study data. The sponsor sub-stratified the safety data for modafinil exposed subjects with greater than or equal to 400 mg/day into subjects with exposure to 400 mg/day and subjects with exposure to greater than 400 mg/day. The sponsor's rationale for this sub-stratification relates to the fact that the highest proposed dose in the draft labeling is 400 mg/day and therefore this dose should be the primary focus of the analysis.

The method for computing dose and duration varied by whether or not the study was conducted by the sponsor

For all six Cephalon –sponsored studies with modafinil dosing of greater than or equal to 400 mg/day, clear, well documented dosing data were available on the CRFs for each study for each subject. For each subject with any study days with a total modafinil dose of at least 400 mg/day, the dosing experience for only those study days with dosing at these levels was

collected. Only adverse experiences that occurred on a study day in which the dose was at least 400 mg/day are included. Adverse experiences are categorized by onset on study days for which the total daily dose was 400 mg and on study days for which total daily dose was greater than 400 mg.

Among the 81 non-Cephalon-sponsored studies with CRFs, only five studies had information linking dosage and study day. Only two of these 5 studies (studies 1424 and 1513) had any modafinil dosing with greater than or equal to 400 mg /day and are therefore included in this analysis of safety data. Categorization of exposure and adverse experience was handled in the same manner as for the Cephalon-sponsored studies.

Among the remaining 76 non-Cephalon-sponsored studies with CRFs, 24 had any dosing with total daily modafinil doses of at least 400 mg/day. Start and stop dates for study drug, dosing and date of adverse experience were not known. Since dose could not be linked to study day in these 24 studies the following methods were followed to determine dosing days greater than or equal to 400 mg/day of modafinil:

NON-CEPHALON-SPONSORED STUDIES WITH FIXED DAILY DOSAGES

- Duration of exposure was ascertained from the CRF
- Dosage the subject was supposed to have received was determined from the protocol instructions

- Subjects were characterized to total days of exposure to either 400 mg/day of greater than 400 mg/day.

- Adverse experiences occurring at any time during the study are included in the analysis

NON-CEPHALON-STUDIES WITH VARIABLE DAILY DOSAGES

- Total daily modafinil dose at each day over the course of the study was calculated.
- Only those subjects with a modal total daily dose of modafinil greater than or equal to 400 mg/day were further analyzed.

- Subjects were categorized into those with modal total daily doses of 400 mg/day and those with modal total daily dose greater than 400 mg/day.

- Adverse experiences occurring at any time during the study are included in the analysis

ANALYSIS

Adverse experience data was categorized by dose (400 mg/day and greater than 400 mg/day) and dosing frequency (once daily and twice daily doses). The sponsor included a third category; a heterogeneous group of non-Cephalon-sponsored studies with variable modafinil dose levels given to individual subjects. This category contains 70 subjects from 15 studies which could not be split into dosing frequency categories because of data limitations.

The sponsor states that the three categories of studies (once daily, twice daily and heterogeneous dosing) are independent and mutually exclusive. The three categories contain

all subjects in the NDA database with total modafinil doses of at least 400 mg/day with once daily or twice daily dosing.

In addition, within both the once daily and twice daily dosing categories, clusters of studies with well documented dosing data were separated from those with less well documented data. Furthermore, clusters of studies were separated by study type; for example the clinical pharmacology studies were analyzed separately.

RESULTS

Corrected Table 1. (Response to FDA Request for Information, Dec. 14, Vol. 1, p. 7)

Exposure to Total Daily Modafinil Dosages Greater than or Equal to 400 mg/day: All Cephalon-Sponsored and Non-Cephalon-Sponsored Studies with Available Databases

DURATION OF EXPOSURE (DAYS)	TOTAL DAILY MODAFINIL DOSAGE (MG)	
	400 N=698	>400 N=146
	N(%)	n(%)
<14	207 (30)	137 (94)
14-28	82 (12)	5 (3)
29-90	83 (12)	4 (3)
91-179	51(7)	0
180-364	182 (26)	0

>364	93 (13)	0

APPEARS THIS WAY ON ORIGINAL

698 subjects received doses of 400 mg/day and 146 received doses of greater than 400 mg/day. Among subjects exposed to 400 mg/day, 326 subjects were dosed for more than 90 days, 275 subjects for at least 180 days, and 93 subjects for at least 365 days. Nearly all exposure at greater than or equal to 400/mgday for more than 90 days is from Cephalon-sponsored Phase 3 studies 301 and 302 (314 subjects). Among subjects treated with greater than 400 mg/day only 9 subjects were dosed more than 14 days. Total exposure to once daily dosing was much greater than total exposure to twice daily dosing (127 subjects). The total number of subjects participating in studies with twice daily dosing was obtained by adding together the numbers of patients exposed to twice daily dosing (Vol. 1, Tables 3.2b and 3.3b, p. 87 and 89).

SINGLE DAILY DOSE AT FIXED DOSAGE

Cephalon-Sponsored Clinical Pharmacology Studies (excluding study 201 AB) sponsor's Table 2.

In the Cephalon-sponsored clinical pharmacology studies, a total of 34 subjects received modafinil doses of 400 mg/day and 36 subjects received modafinil doses of >400 mg/day. Many adverse experiences, including headache, asthenia, nausea, anorexia, insomnia, nervousness, and abnormal thinking were more frequent at >400 mg/day than at 400 mg/day. Only euphoria was noticeably more frequent at 400 mg/day than at >400 mg/day.

Cephalon-Sponsored Clinical Pharmacology Study 201 AB sponsor's Tables 3A and 3B

In the only single (once) daily dose non-Cephalon-sponsored study with known start and stop dates for study drug and adverse experiences a total of 12 subjects received modafinil at 400 mg/day for 1-2 days. Two subjects (17%) experienced headache.

Non-Cephalon-Sponsored Studies With Unknown Start and Stop Dates for Study Drug and Adverse Experiences (one study, short duration) sponsor's Table 4.

In this single (once) daily dose non-Cephalon-sponsored study with unknown start and stop dates for study drug and adverse experiences, 30 subjects received 400 mg/day and no subjects received > 400 mg. This was a short-term study (no more than 2 days exposure) and the most common adverse experience was headache (23%).

SINGLE DAILY DOSE AT VARIABLE DAILY DOSES

Cephalon-Sponsored Phase 3 Studies; Open-Label Phases sponsor's Table 5

In the Cephalon-sponsored open-label studies a total of 405 subjects received doses of modafinil of 400 mg/day and only 15 subjects received at least one daily dose of modafinil > 400 mg/day. No subject received modafinil > 400 mg/day for more than 13 days. The most common adverse experience at 400 mg/day was headache (46%). The next most common adverse experiences (with frequencies > 10%) were infection (31%), rhintis (17%), pain (16%), dyspepsia (15%), flu syndrome (14%), tooth disorder (13%), accidental injury (12%), back pain (11%), and sinusitis (11%).

TWICE DAILY DOSE AT FIXED DAILY DOSAGES

Non-Cephalon-Sponsored Study With Known Start and Stop Dates for Study Drug and Adverse Experiences (protocol 1424) sponsor's Table 6.

In the only twice daily dosing non Cephalon-sponsored study with known start and stop dates for study drug and adverse experiences, 8 subjects received modafinil 400 mg and 22 received modafinil > 400 mg. The most common adverse experience with 400 mg/day dosing was the adverse reaction term CNS stimulation (88%). Headache was the second most common adverse experience (63%). At > 400 mg/day, headache and the adverse reaction term personality disorders were the most common adverse experiences, with frequencies of 59% and 50%, respectively. In this study, the number of adverse experiences that were more common with 400 mg/day of modafinil was nearly equal to the number of adverse experiences that were more frequent at > 400 mg/day.

Non-Cephalon-Sponsored Studies With Unknown Start and Stop Dates for Study Drug and Adverse Experiences sponsor's Table 7.

In the twice daily dose non-Cephalon-sponsored studies with unknown start and stop dates for study drug and adverse experiences, 80 subjects received modafinil 400 mg/day and 17 subjects received modafinil > 400 mg/day. No subject received >400 mg/day for more than seven days. For all the adverse experiences in this table, the frequency of the adverse experience was higher with > 400 mg/day. Unlike other studies, the frequency of headache at 400 mg/day was very low, 3%.

APPEARS THIS WAY ON ORIGINAL

MULTIPLE (VARIABLE) DOSE ADMINISTRATION LEVELS

Non-Cephalon-Sponsored Studies with Unknown Start and Stop Dates for Study Drug and Adverse Experiences, sponsors Table 8.

In the multiple daily dose non-Cephalon-sponsored studies with unknown start and stop dates for study drug and adverse experiences, 42 subjects received modafinil 400 mg/day and 28 received modafinil > 400 mg/day. The most common adverse experience in the 400 mg/day and > 400 mg/day group was insomnia with a frequency of 21% and 62%, respectively. The majority of adverse experiences were more frequent at > 400 mg/day of modafinil than at 400 mg/day.

SPONSOR'S CONCLUSIONS

Treatment with total modafinil doses of 400 mg/day was well tolerated in all categories of studies. Further evidence that 400 mg/day is well tolerated is provided by the fact that of 302 subjects who received modafinil 400 mg/day for more than 90 days in the open-label phases of study 301 and 302, the rate of discontinuation for adverse experiences was 3%, while overall discontinuation rate for all subjects in the open-label phases of these studies was 10%.

Almost all of the modafinil dosing at a dosage of 400 mg/day in studies other than studies 301 and 302 (including their open-label phases) was short-term.

In studies with short-term modafinil dosing (<90 days) at dosages >400 mg/day, the types of adverse experiences that were most commonly observed were generally similar across

TWICE DAILY DOSE AT FIXED DAILY DOSAGES

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SPONSOR'S CONCLUSIONS

Treatment with total modafinil doses of 400 mg/day was well tolerated in all categories of studies. Further evidence that 400 mg/day is well tolerated is provided by the fact that of 302 subjects who received modafinil 400 mg/day for more than 90 days in the open-label phases of study 301 and 302, the rate of discontinuation for adverse experiences was 3%, while overall discontinuation rate for all subjects in the open-label phases of these studies was 10%.

Almost all of the modafinil dosing at a dosage of 400 mg/day in studies other than studies 301 and 302 (including their open-label phases) was short-term.

In studies with short-term modafinil dosing (<90 days) at dosages >400 mg/day, the types of adverse experiences that were most commonly observed were generally similar across

study categories and dosing frequency. With continued (long-term) treatment, the new adverse experiences seen were to a large extent those of daily life.

Adverse experience frequencies observed with total daily modafinil doses of >400 mg/day were generally greater than those seen with 400 mg/day and were usually of the same type.

The subject exposure to 400 mg/day of modafinil was much greater than the exposure to >400 mg/day. This was true both for the number of subjects exposed (698 at 400 mg/day and 146 at >400 mg/day) and also the duration of exposure (409 subjects at 400 mg/day for more than 28 days vs. 4 subjects at >400 mg/day for more than 28 days).

The total exposure to once daily modafinil dosing at dosages greater than or equal to 400 mg/day was much greater than exposure to subjects to twice daily dosing. No valid comparison could be made of the adverse experience profiles of once daily vs. twice daily dosing for at least two reasons. All the dosing in U.S. studies was once daily, while most European studies were twice daily and therefore confounded by cultural differences in adverse experience reporting, Secondly, the adverse experience frequencies were too variable within both the once daily and twice dosing categories to allow meaningful comparisons between them.

REVIEWER'S COMMENTS

In general the quality and completeness of data from non-Cephalon-sponsored studies (foreign) used by the sponsor in this submission are inferior to that of the Cephalon sponsored studies (U.S.). Limitations in the comparison of Cephalon-sponsored versus non-sponsored

studies may be more due to differences in data collection and quality rather than cultural differences in adverse experience reporting as the sponsor suggests.

Nearly all the long term safety data is from the open-label phases of studies 301 and 302 which were conducted with a once daily dosing schedule. The overall number of subjects exposed to modafinil at doses greater than or equal to 400 mg a day for greater than 1 year is 93. There is limited data on subjects exposed to twice daily dosing (127 subjects, only 8 of whom completed more than 28 days of treatment).

For the non-Cephalon-sponsored studies in which subject eligibility for analysis was determined by the subject's modal dose of modafinil over the course of the study, the potential exists for including adverse experiences with onset at times for which the total daily modafinil dose was less than 400 mg/day. The sponsor considers inclusion of all adverse experiences for subjects in such studies to be a conservative approach to data analysis. While to some extent this assumption is reasonable, the inclusion of events at all dose levels blurs any qualitative or quantitative differences among specific dose levels.

The sponsor states that long term safety is further evidenced by the fact that the discontinuation rate due to adverse experiences was only 3% in subjects exposed to 400 mg/day for more than 90 days verses a 10% discontinuation rate for all subjects in the open-label phase of studies 301 and 302. While reassuring, a declining discontinuation rate due to adverse experiences as the study progresses might normally be expected. Discontinuation of subjects early in the course of a study due to adverse experiences pre-selects for a more

medication tolerant cohort which is then able to progress further on in the study and may be able to tolerate higher doses of the study drug.

Overall there is a limited degree of experience with modafinil exposure at greater than or equal to 400 mg/day for more than 90 days (326 subjects 314 of which are from the open-label phases of studies 301 and 302) and at greater than 364 days (93 subjects). The sponsor has not specifically stratified adverse experiences by duration of therapy, nor has the sponsor categorized reports by level of seriousness. The majority of the long-term experience is derived from the open-label phases of studies 301 and 302. A more detailed review of these studies will be accomplished in the review of the updated integrated summary of safety.

3. Please submit available laboratory data for the foreign studies. Describe in detail how often laboratory measurements were assessed in the various foreign cohorts.

SUMMARY OF SPONSORS RESPONSE

SOURCE VOL. 3 OF 67,

METHODS

All non-Cephalon-sponsored clinical study reports, data summaries, subject listings, available databases, and all case report forms, were reviewed to determine the studies in which laboratory data had been collected. Laboratory data from 25 studies sponsored by [redacted] were identified. Five of these studies only had laboratory data collected at baseline.

[redacted]

Only those 20 studies containing laboratory data for on- or post-treatment assessments are included by the sponsor in this review.

The analysis of clinical laboratory tests was preformed by study. The integrated analyses focuses on clinically significant abnormalities only. The criteria for the clinically significant abnormalities is based on the cut points from FDA Division of Neuropharmacological Drug Products and modified by Cephalon (Vol. 3, Appendix 2.0, p. 62). Patients with clinically significant laboratory values on modafinil treatment that were also present before modafinil treatment are not discussed in the narrative section for each individual study.

The sponsor performed 100% quality control checks on all data entered into the laboratory database. Those errors identified were corrected.

RESULTS

A total of 686 subjects are summarized, 525 with modafinil treatment and 161 placebo-treated subjects. There were 452 male and 230 female patients ranging in age from 12-90 years.

The most frequently occurring clinically significant abnormal laboratory values for all assessments were hematocrit (149 values), hemoglobin (87 values), red blood cells (76 values), lymphocytes (42 values), bicarbonate (36 values), glucose (34 values), WBC (34 values), and BUN (32 values). All other clinically significant abnormal values had a frequency of less than 25.

SPONSORS CONCLUSIONS

Review of all laboratory data from non-Cephalon-sponsored studies revealed no clinically meaningful average laboratory values or trends in the occurrence of abnormal laboratory values.

COMMENTS

At the request of the FDA the sponsor provided additional information on patients with clinically significant elevations of liver enzymes (total bilirubin, GGT, alkaline phosphatase, ALT and AST). This information is provided in a Response to FDA Request for Information Dated December 14, 1988.

A total of 27 patients participating in 10 studies conducted by Laboratoire L. Lafon experienced a clinically significant liver enzyme elevation either pre-treatment, on placebo or while receiving modafanil. Among these 27 patients only 10 had documented clinically significant liver enzyme elevations either prior to and during modafanil treatment (Attachment 2).

Four patients had clinically significant elevations prior to modafanil treatment. Two of these 4 patients with clinically significant elevations were enrolled in study MOD-021, a PK study in patients with severe chronic hepatic insufficiency. There did not appear to be any consistent treatment related trends among these patients.

Six patients developed new onset clinically significant liver enzyme elevations. In three patients the liver enzyme was elevated prior to treatment. In four patients enzyme elevations appeared to be resolving at endpoint.

The abnormalities of hematocrit, hemoglobin and RBC are co-related and of uncertain significance as are several instances of low lymphocyte values. The sponsor appears to have made a reasonable effort to abstract and present the available laboratory data from the non-Cephalon-sponsored studies. No clinical concern is raised from the available data.

/S/

Joel Freiman, M.D.

R. Katz

APPEARS THIS WAY ON ORIGINAL

HFD-120

NDA, 20-217

HFD-120, Freiman, Katz, Hommonay