

DOCUMENT INFORMATION PAGE

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END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.



NDA 20-717/S-019

Cephalon, Inc.
Attention: James Ciciriello
41 Moores road
P.O. Box 4011
Frazer, PA 19355

Dear Mr. Cicirello:

Please refer to your supplemental new drug application dated and received December 20, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Provigil (modafinil) Tablets.

We acknowledge receipt of your additional submissions dated:

April 13, 2005

May 24, 2005

August 29, 2005

April 19, 2005

August 23, 2005

September 14, 2005

This supplemental new drug application provides for the use of modafinil for Attention-Deficit Hyperactivity Disorder (ADHD) and a revised drug product formulation including the following new strengths: 85 mg, 170 mg, 255 mg, 340 mg, and 425 mg.

We have completed our review of this application, as amended, and it is potentially approvable. Before the application may be approved, however, you must address the following deficiencies:

Specific Safety Requests

We have several specific safety concerns that need to be further addressed:

1. Serious Rash

There were 3 cases of clinically important rash among 933 patients exposed to modafinil in your modafinil/ADHD program.

-One of these was a 7 year old male (062338) who was noted to have a sore throat, fever and mild rash by day 16 of treatment with modafinil 340 mg/day. Amoxicillin was started on day 17, but apparently was limited to a single dose. The modafinil was also stopped by day 17. By day 19, the rash was spreading, and continued to progress, with blistering, peeling, and mucosal involvement (lips and urethral meatus). A dermatologist made a diagnosis of Stevens-Johnson. The rash appeared to resolve by day 30. No skin biopsy results were reported. Our consulting dermatologist suggested trying to obtain RAST testing for penicillin allergy for this patient. Given the limited data available, modafinil cannot be ruled out as a possible cause of this serious event.

-A second case involved an 11 year old female (315) with a maculopapular rash that developed on day 4 of treatment. The patient was treated with diphenhydramine, but the rash worsened and the patient was hospitalized on day 15. A dermatologist considered this to represent a morbilliform rash and treated it with an antihistamine. It resolved within a week.

-A third case involved an 8 year old male (180004) with mild fever, rash on the cheeks and severe blisters on the lips by day 14 of treatment. Modafinil was stopped at this point, and the rash resolved.

There were also less significant rashes, and overall, the incidence of rash in the three phase 3 trials was 4% for modafinil and 2% for placebo.

We are also aware of 5 AERS reports of either erythema multiforme or Stevens-Johnson in adults treated with modafinil.

Comment: Finding even a single case of Stevens-Johnson in a small controlled trials experience is of concern, given how rare this event is as a background event. The finding of 5 AERS reports of either erythema multiforme or Stevens-Johnson adds to the concern that the Stevens-Johnson case in the controlled trial may have been related to modafinil use. We ask that you obtain whatever additional information might be available for this case, e.g., a skin biopsy if obtained and RAST testing for penicillin allergy, if feasible. We further note that the presence of excess levels of the sulfone metabolite in children compared to adolescents and adults suggests the possibility of sulfone allergy as a possible mechanism for this event, and you may consider further evaluation of this possibility. You may also consider getting your own expert dermatological consultation on these cases. Finally, we ask that you propose labeling to appropriately warn of the risk of serious skin rash. In the absence of a better understanding of these events, we consider a warning statement to be the appropriate level for this event, along with clear advice to seek medical attention at the first sign of a rash.

2. Psychiatric Adverse Events

Although your 2% adverse event table (Table 2 in your proposed label) does not identify any psychiatric events as showing an excess for drug compared to placebo, it is striking when assessing dropouts for psychiatric adverse events that almost all of the dropouts for certain psychiatric adverse events occurred in modafinil-treated patients. These events included suicidal ideation, agitation, depression, and psychosis. In addition, we note that, in certain instances, the coding of events leading to discontinuation seemed to incorrectly classify the event. For example, patient 14016 in study 311 was categorized as a dropout for "personality disorder" when the behavior described as leading to discontinuation involved placing a rope around his neck. This example raises a concern about the coding of psychiatric adverse events in this program. In general, there have been recent concerns raised about psychiatric adverse events occurring in association with drugs used to treat ADHD. In fact, the agency sent request letters on 9-15-05 asking sponsors of approved ADHD products and several drugs under development for ADHD to re-examine their controlled trials databases for psychiatric adverse events (Cephalon received such a request for modafinil trials in ADHD). Given this concern, we ask that, as part of your response to this action letter, you complete this requested search for your modafinil trials, and in addition, that you conduct appropriate analyses of the data accumulated in this search for psychiatric adverse events. As part of this exploration for psychiatric adverse events, we ask that you re-consider the coding of psychiatric adverse events in your program to ensure that this was done appropriately.

3. Transaminase Elevations

Although the controlled trials data did not reveal a signal for drug-related mean increase in transaminase values or in drug-related outliers, there were 3 modafinil-treated patients who had transaminase increases of concern but insufficient other information to further assess the significance of these changes:

-Patient 056003: This was a 9 year old male who developed fever, generalized hives, and vomiting on day 13 of modafinil treatment. Treatment was stopped, but on day 14 he was noted to have an ALT of 517 U/L and AST of 409 U/L. These levels returned to normal by days 23 and 35 respectively.

-Patient 63329: This was a 17 year old male with an ALT of 453 U/L and AST of 269 U/L.

-Patient 006120: This was a 9 year old male with an AST of 262 U/L.

Please determine if bilirubin values were obtained for these patients, and if so, provide these and any other relevant clinical data that would help in determining the seriousness of these cases.

Chemistry Requests

- Please explain the differences in the ester purity levels and the specific rotation values obtained at and
- Pl used in the manufacture of the drug product at .
- Please provide updated drug product stability data from .

Biopharmaceutics Requests

-
-
- You have shown in vitro that modafinil and modafinil sulfone have the potential to induce CYP3A4 using nifedipine as substrate and CYP2C9 using phenacetin as a substrate with human hepatocytes. In the future, in addition to assessing the potential to induce CYP2C9 and CYP2C19, the potential to induce CYP2C8 should also be evaluated. Please refer to the Guidance for Industry: Drug Interaction Studies: Study Design, Data Analysis, and Implications for Dosing and Labeling when planning for future studies.

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt upon approval of this supplemental application. The base document used for our draft labeling is your

labeling submitted on December 20, 2004. Please also note that we have embedded throughout the text of the attached draft labeling several comments and further revisions of the labeling. We also ask that when you submit draft labeling, you include in the labeling all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, use a clean copy of the draft labeling attached to this letter as a base document, and provide a highlighted or marked-up copy that shows all changes, both deletions and additions, to this base document. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

You should also be aware that there will likely be multiple additional changes to labeling based on your responses to our requests for additional specific safety information and for a safety update.

Division of Medication Errors and Technical Support (DMETS) Requests

Dual Tradename Issues: You propose to market modafinil tablets under two proprietary names, Provigil and for this pending application, Sparlon. In essence, if approved, modafinil will be available from the same manufacturer with two different names (Provigil and Sparlon). Confusion may arise if practitioners are not aware that Provigil and Sparlon are the same drug product. Additionally, we are concerned that the use of the name Sparlon may result in concomitant administration of both products or be administered to a patient with a documented allergy, hypersensitivity, or intolerance to the active ingredient not knowing both products contain the same active ingredient. Please note that your proposed name, Sparlon, will be reviewed again when you respond to this action, however at this time it is acceptable.

1. Risk Minimization Recommendations: In order to avert dual tradename prescribing, we suggest the following:
 - a. You should devise a plan that would monitor concomitant administration of these products and the adverse events associated with the concomitant use of both drug products postmarketing.
 - b. Disseminate a Dear Healthcare Provider letter that informs all types of healthcare providers that Provigil and Sparlon are the same drug product with the same adverse event profile. Additionally, you should institute an education campaign that includes professional journal ads.
 - c. Institute a public educational campaign to inform the public community that Sparlon is the same drug as Provigil. This would provide global information to the community that the same safety concerns that are seen with Provigil would expect to be seen with Sparlon.
 - d. Ensure the Sparlon package insert contains the same warning and precautions as Provigil. Additionally, the insert labeling should state “Patients should be aware that SPARLON contains the same active ingredient found in PROVIGIL, used to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep/apnea/hypopnea syndrome, and shift work sleep disorder, and that SPARLON should not be used in combination with PROVIGIL or any other medications that contain modafinil.”
 - e. Place a statement on the container labels and carton labeling that indicates Provigil and Sparlon are the same drug product and should not be used concomitantly.

2. Labels and Labeling: In the review of the labels and labeling, we have attempted to focus on safety issues relating to possible medication errors. Please provide revised labeling for the name Sparlon.
 - a. CONTAINER LABEL
 - i. Place a statement on the container labels and carton labeling that indicates Provigil and Sparlon are the same drug product and should not be used concomitantly.
 - ii. The “CIV” located to the right of the proprietary name is large in font size and looks like it is part of the proposed name. We recommend decreasing the font size of the control symbol and locating it further to the right of the proprietary name so it appears separate from the name.
 - iii. The “mg” in the strength should be separated by a space from the numerical strength and revised to be in the same font size as the numerical strength. In addition, we believe that the strength would be more appropriately located following the proprietary and established names. Once relocated, please ensure that the net quantity appears away from the product strength in order to avoid confusion between the various numerical values.
 - iv. Due to the black and white presentation of the labels and labeling, we are unable to determine if the multiple strengths are clearly differentiated from one another. Please ensure that the multiple strengths are clearly differentiated by the use of a contrasting color, boxing, or some other means. Provide a color copy with your response to this action.
 - v. According to 21 CFR 201.55, a “Usual Dosage” statement must appear on the label. Revise accordingly.
 - b. BLISTER LABEL (Professional Sample)
 - i. See comments above (2a, i-iv).
 - ii. The net quantity statement on the front display panel “Contains 7 tablets 85 mg” is confusing and may lead to error. Please delete the product strengths from the net quantity statement and label as “Contains 7 tablets”.
 - iii. Additionally, for all strengths, the following statement should appear on the primary display panel: “Each tablet contains XX mg of Modafinil”.
 - c. CARTON LABELING (Professional Sample)
 - i. See comments above (2a, i-iv).
 - d. PACKAGE INSERT: Ensure the Sparlon package insert contains the same warning and precautions as Provigil. Additionally, the insert labeling should state “Patients should be aware that SPARLON contains the same active ingredient found in PROVIGIL, used to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep/apnea/hypopnea syndrome, and shift work sleep disorder, and that SPARLON should not be used in combination with PROVIGIL or any other medications that contain modafinil.”

Safety Update

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Psychiatry Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

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If you have any questions, call Richardae Taylor, Pharm.D., Regulatory Project Manager, at (301) 796-1152.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

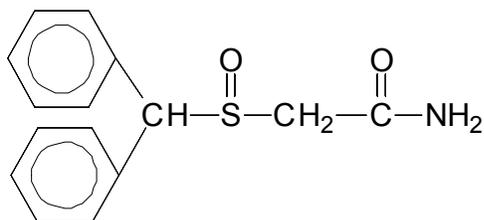
Enclosure

[This draft of labeling was created using the clean draft of labeling submitted with the NDA in December, 2004. We have used track changes to denote all deletions and additions. Bracketed comments are included preceding changes that are not self-explanatory. Bracketed comments are also used to request additional data, analyses, or labeling language that we feel are needed. We note that the proposed name "SPARLON" has been deemed acceptable, and you will need to replace the name ATTENACE with SPARLON in your proposed label in response to this document. In addition, as noted in the letter, you will need to update the label with relevant changes to Provigil labeling that have been made since December, 2004.]

ATTENACE™ (modafinil) Tablets [C-IV]**Rx Only****DESCRIPTION**

ATTENACE (modafinil) is an orally administered agent for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). Modafinil was initially developed and is also marketed as a wakefulness-promoting agent PROVIGIL® Tablets. Modafinil is a racemic compound. The chemical name for modafinil is 2-[(diphenylmethyl)sulfinyl]acetamide. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.356.

The chemical structure is:



Modafinil is a white to off-white, crystalline powder that is very slightly soluble in water and practically insoluble in cyclohexane. It is sparingly soluble in methanol and slightly soluble in acetone. ATTENACE tablets contain 85, 170, 255, 340, or 425 mg of modafinil and

the following inactive ingredients: lactose, croscarmellose sodium, povidone, and ~~non-bovine~~ magnesium stearate. The film coating for all tablet strengths contains: hypromellose, titanium dioxide, lactose, polyethylene glycol, and triacetin. In addition, the 170 mg and 340 mg tablets contain iron oxide yellow, and the 255 mg and 425 mg tablets contain FD&C Blue#2.

CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacology

[We have made extensive changes to this section. In the second paragraph below, we have excluded the phrases “with weak affinity” (in reference to binding to the dopamine reuptake site) and “unlike amphetamines” (in reference to increasing dopamine release) which you added. Please submit data to justify these phrases if you wish to have them included].

The precise mechanism(s) through which modafinil produces its therapeutic effects is unknown. Modafinil has ~~stimulant wake-promoting~~ actions similar to sympathomimetic agents like amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of sympathomimetic amines.

Modafinil is not a direct acting dopamine receptor agonist as evidenced by its lack of activity in several *in vivo* preclinical assays capable of measuring enhanced dopaminergic activity. *In vitro*, modafinil binds to the dopamine reuptake site, causing an increase in extracellular dopamine, but does not increase dopamine release. In a preclinical model, the wakefulness induced by amphetamine, but not modafinil, is antagonized by the dopamine receptor antagonist haloperidol.

Modafinil has weak to negligible interactions with receptors for norepinephrine, dopamine, GABA, adenosine, histamine-3, melatonin, and benzodiazepines. Modafinil also does not inhibit the activities of MAO B or phosphodiesterases II - V.

In humans, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; modafinil was also partially discriminated as stimulant-like.

~~Modafinil is not a direct acting dopamine receptor agonist as evidenced by its lack of activity in several *in vivo* preclinical assays capable of measuring enhanced dopaminergic activity. *In vitro*, modafinil binds with weak affinity to the dopamine reuptake site, causing an increase in extracellular dopamine, but unlike amphetamines, does not increase dopamine release. In a preclinical model, the wakefulness induced by amphetamine, but not modafinil, is antagonized by the dopamine receptor antagonist haloperidol.~~

~~Modafinil does not appear to be a direct or indirect α_1 -adrenergic agonist. Although modafinil-induced wakefulness can be attenuated by the α_1 -adrenergic receptor antagonist, prazosin, in assay systems known to be responsive to α -adrenergic agonists, modafinil has no activity. Modafinil does not display sympathomimetic activity in the rat vas deferens preparations (agonist-stimulated or electrically stimulated) nor does it increase the formation of the adrenergic receptor-mediated second messenger phosphatidyl inositol in *in vitro* models. Unlike sympathomimetic agents, modafinil has minimal effects on cardiovascular and hemodynamic parameters.~~

~~In the cat, equal wakefulness-promoting doses of methylphenidate and amphetamine increased neuronal activation throughout the brain. Modafinil at an equivalent wakefulness-promoting dose selectively and prominently increased neuronal activation in more discrete regions of the brain. The relationship of this finding in cats to the effects of modafinil in humans is unknown.~~

~~In adults, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; modafinil was also partially discriminated as stimulant-like.~~

The optical enantiomers of modafinil have similar pharmacological actions in animals. Two major metabolites of modafinil, modafinil acid and modafinil sulfone, do not appear to contribute to the CNS-activating properties of modafinil.

Pharmacokinetics

In adults, the pharmacokinetics of modafinil are proportional over the dose range of 200-600 mg/day; with an elimination half-life of approximately 15 hours. Dose proportionality is also

evident in children and adolescents as suggested by population pharmacokinetic analysis. In children, modafinil half-life tends to be shorter than in adults. However, as children age through adolescence and into young adulthood, modafinil pharmacokinetics become more similar to that of adults.

Modafinil is a racemic compound, whose enantiomers have different pharmacokinetics (e.g., the half-life of the *l*-isomer is approximately three times that of the *d*-isomer in adult humans). The enantiomers do not interconvert. [With repeated dosing in healthy adults](#)~~At steady state~~, total exposure to the *l*-isomer is approximately three times that for the *d*-isomer.

Absorption

Modafinil is well absorbed after oral administration, with bioavailability of the tablet formulation being approximately equal to that of an aqueous suspension. Absolute bioavailability was not determined due to the aqueous insolubility (<1 mg/mL) of modafinil, which precluded intravenous administration. The t_{max} in adults is, on average, approximately 2 to 4 hours. In children and adolescents, the t_{max} is 2 to 3 hours. Data in healthy adults indicate that food affects the rate, but not the extent, of absorption.

Distribution

Modafinil is lipophilic in nature and is well distributed beyond the vascular system ($V/F \sim 0.9$ L/kg) in adults. Modafinil is also well distributed in children, although it is important to note that body weight has a significant effect on V/F in children and adolescents, with volume of distribution increasing in a linear manner with weight. Modafinil is moderately protein bound (approximately 60%), mainly to albumin. Therefore, the potential for interactions with highly protein-bound drugs is minimal.

Metabolism

Modafinil is almost exclusively metabolized by the liver, with less than 10% of the administered dose excreted unchanged in the urine. Modafinil is primarily metabolized via a hydrolytic pathway and, to a lesser extent, via oxidative pathways. Metabolism occurs through hydrolytic deamidation, S-oxidation, aromatic ring hydroxylation, and glucuronide conjugation. In a clinical study conducted in healthy adults using radiolabeled modafinil, 81% of the administered dose was recovered over the 11-day study period, predominantly in the urine (80%) versus the feces (1%). Greater than 90% of the urinary radioactivity was excreted within 24 hours of

administration. The major radioactive form that was recovered in urine was modafinil acid (40%), with at least 6 other metabolites present in lower concentrations. Alkalinization of the urine did not affect urinary excretion of modafinil or its primary circulating metabolites, modafinil acid and modafinil sulfone.

Following repeat-dose administration of modafinil, a time-dependent reduction in modafinil systemic exposure is observed in children/adolescents [through autoinduction of CL/F](#). Plasma concentrations of one of modafinil's metabolites, modafinil sulfone, following multiple-dose administration of modafinil was often notably higher in children than that previously observed in adults. In vitro data have shown that modafinil sulfone has the potential to induce CYP-mediated metabolism, including that of modafinil itself, which could contribute to the observed reduction in systemic exposure to modafinil following repeat-dose administration.

Elimination

The pharmacokinetic disposition of modafinil changes as children age through adolescence and into young adulthood. Children 6 to 7 years of age exhibit a half-life of approximately 7 hours with half-life approaching that of adults as children age [\(half-life of 15 hours\)](#). Following repeat-dose administration of modafinil, a time-dependent reduction in systemic exposure as a result of change in clearance over time is observed in children/adolescents. Population pharmacokinetic modeling in children/adolescents indicates that the increase in clearance reaches a plateau by approximately week 6 of treatment [\(with an induction half-life of about 12 days\)with modafinil](#) and, as a result, measurements performed at week 9 are reflective of steady state. ~~[Once steady state is reached, the pharmacokinetic properties of modafinil do not change with continued administration of modafinil for up to 1 year.](#)~~

Drug-Drug Interactions: Based on *in vitro* data, modafinil is metabolized partially by the 3A isoform subfamily of hepatic cytochrome P450 (CYP3A4). In addition, modafinil has the potential to inhibit CYP2C19 and induce CYP3A4, CYP2B6, and CYP1A2. Because modafinil and modafinil sulfone are reversible inhibitors of the drug-metabolizing enzyme CYP2C19, co-administration of modafinil with drugs such as diazepam, phenytoin and propranolol, which are largely eliminated via that pathway, may increase the circulating levels of those compounds. In addition, in individuals deficient in the enzyme CYP2D6 (i.e., 7-10% of the Caucasian population; similar or lower in other populations), the levels of CYP2D6 substrates such as

tricyclic antidepressants and selective serotonin reuptake inhibitors, which have ancillary routes of elimination through CYP2C19, may be increased by co-administration of modafinil. Dose adjustments may be necessary for patients being treated with these and similar medications (See **PRECAUTIONS, Drug Interactions**).

Special Populations

The effect of gender, age, and weight on modafinil pharmacokinetics in children and adolescents with ADHD were examined using a population pharmacokinetic approach.

Gender Effect: The pharmacokinetics of modafinil are not affected by gender.

Age Effect: The estimated $t_{1/2}$ for the youngest patients (aged 6 to 7 years) studied is approximately 7 hours, and the $t_{1/2}$ for the oldest patients (aged 16 to 17 years) is approximately 10 hours. The general trend in the data indicates that there is a shift that begins between 9 and 11 years of age towards an increase in $t_{1/2}$.

Weight Effect:

In children and adolescents, body weight has a significant effect on both clearance and volume of distribution of modafinil. Volume of distribution increases linearly with weight. Clearance also increases with increasing weight ~~up to approximately 30 kg, after which clearance remains relatively constant with increasing weight.~~

Based on these data, a modafinil dose of 340 mg in children and adolescents weighing less than 30 kg and 425 mg in children and adolescents weighing 30 kg or more consistently results in similar systemic exposures, indicating that the use of weight as a surrogate for dose selection is appropriate (See **DOSAGE and ADMINISTRATION**).

Race Effect: Modafinil pharmacokinetics are similar between Caucasian and African American populations. However, there were a limited number of patients in other race groups in the clinical trials which makes it difficult to fully elucidate any potential effect in these subgroups (approximately 90% of patients were Caucasian and African American).

Renal Impairment: In adults, severe chronic renal failure (creatinine clearance up to 20 mL/min) did not significantly affect the pharmacokinetics of modafinil administered at 200 mg, but exposure to modafinil acid was increased 9-fold (See **PRECAUTIONS**). No renal impairment studies have been conducted in children or adolescents.

Hepatic Impairment: Because modafinil is exclusively metabolized in the liver, hepatic impairment is expected to have an impact on the pharmacokinetic profile of the compound. Adult patients with cirrhosis have a decreased ability to metabolize modafinil, compared with healthy subjects. The oral clearance of modafinil was decreased by approximately 60%, and the steady-state concentration doubled, compared with values in healthy subjects. These results indicate that the dosage of modafinil should be reduced in patients with severe hepatic impairment (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). No hepatic impairment studies have been specifically conducted in children or adolescents.

Pharmacodynamics

Clinical trial data indicate that administration of 340 mg of modafinil in children and adolescents with body weights less than 30 kg and 425 mg of modafinil in children and adolescents with body weights greater than or equal to 30 kg, achieve a sustained systemic exposure (approximately 150 µg/mL) which correlates with a clinically significant effect. ~~A less than optimal response is observed with inadequate systemic exposures. Over time, there were no~~ observed trends towards a change in exposure or clinical effect with chronic dosing over 21 weeks.

CLINICAL TRIALS

[We have made a number of changes to this section:

-We have limited the description of findings to the protocol specified primary endpoints, thus, we have deleted references to subscales.

-We do not feel the score changes are clinically interpretable or useful, thus, we have deleted the table and figure.

-We have deleted the reference to a lack of rebound effect because we consider this safety information that, in fact, has already been included in Drug Abuse and Dependence.

The effectiveness of ATTENACE in the treatment of ADHD was established in 3 randomized, double-blind, placebo-controlled studies of children and adolescents (ages 6 to 17) who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD (See **INDICATIONS and USAGE**).

Patients included in the phase 3 placebo-controlled studies were at least moderately ill according to the Clinical Global Impression of Severity (CGI-S) of ADHD symptoms. At baseline, 86% of the patients were moderately or markedly ill, and 14 % were severely ill. As measured by the Diagnostic Interview Schedule for Children, 4th edition (DISC-IV), 30% of the patients had the inattentive subtype, 5% had the hyperactive/impulsive subtype, while 65% of the patients had the combined subtype of ADHD. All baseline demographic characteristics were similar for patients in the ATTENACE and placebo treatment groups. Of the 621 patients who received study drug, 71% were boys, and 76% of the patients were Caucasian. The mean age of the patients was 10.1 years (range 6 to 17 years); and most patients (67%) were less than 12 years of age. The mean weight was 41.4 kg (range 18.6 to 98.4 kg), with 68% of the patients weighing at least 30 kg.

In all studies, the primary assessment of efficacy was the total score from the teacher/physician-completed ADHD Rating Scale-IV (ADHD-RS-IV) (School Version). The primary outcome measure was the comparison of the mean change from baseline to endpoint for ATTENACE- and placebo-treated patients. The ADHD RS-IV assesses the frequency of each of 18 individual criteria symptoms of ADHD in the DSM-IV on a 4-point Likert scale (0=never or rarely, 1=sometimes, 2=often or 3=very often). The ADHD-RS-IV (School Version) was completed by the investigator through interviewing the patient's weekday teacher.

In 2 identical, 9-week, randomized, double-blind, placebo-controlled, flexible-dosage studies of children and adolescents aged 6 to 17 (Study 1, N=200; Study 2, N=248), patients were randomized on a 2:1 basis to received either ATTENACE or placebo. ATTENACE was administered as a single morning dose and titrated on a weekly basis, according to clinical response and tolerability, up to a maximum of 425 mg. Statistically significant improvements in ADHD symptoms were observed in ATTENACE-treated patients compared with placebo-treated patients as measured by ADHD-RS-IV (School Version) total score, [including the hyperactive/impulsive and inattentive subscales \[Table 1\]](#).

In Study 3, a 9-week, randomized, double-blind, placebo-controlled, fixed-dosage study of children and adolescents aged 6 to 17 (N=198), patients received either ATTENACE (340 or 425 mg) or placebo. Patients weighing less than 30 kg received 340 mg of ATTENACE and patients weighing at least 30 kg received 425 mg of ATTENACE or matching placebo. Treatment was administered once daily and titrated to the fixed dose during the first 7 to 9 days. Statistically significant improvements in ADHD symptoms were observed in ATTENACE-treated patients compared with placebo-treated patients as measured by ADHD-RS-IV (School Version) total score, including the hyperactive/impulsive and inattentive subscales [Table 1]. The final 2 weeks of Study 3 was a randomized withdrawal period during which no rebound effect following the abrupt discontinuation of ATTENACE was reported.

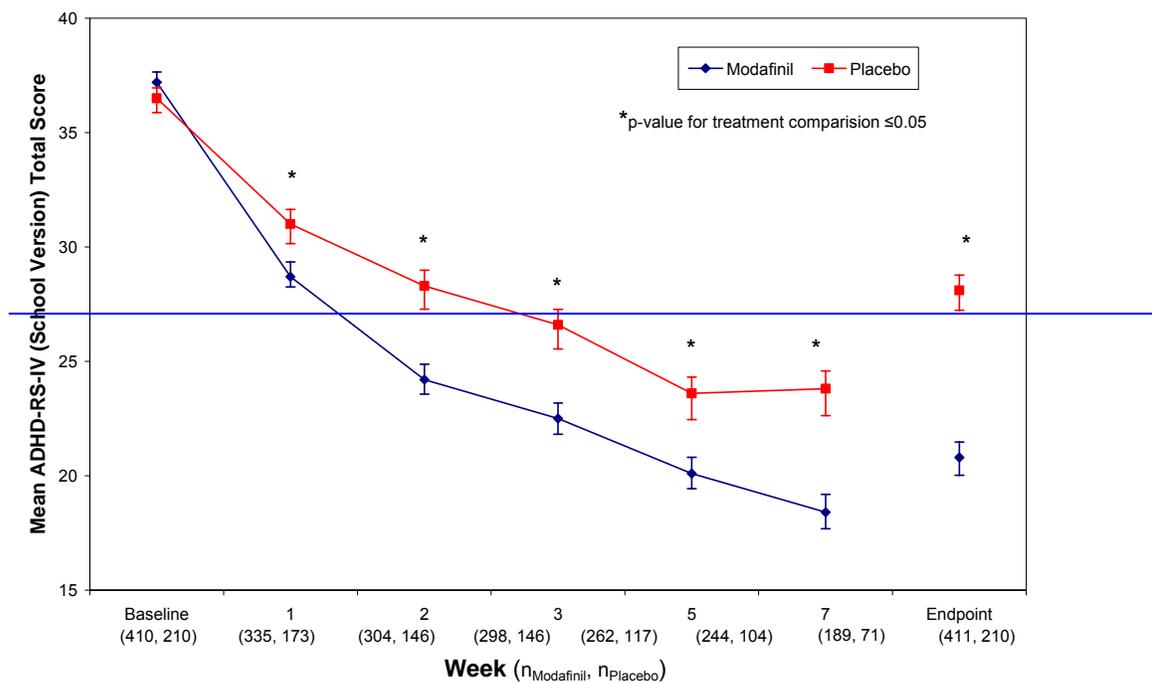
In the pooled data across all 3 studies, statistically significant differences between patients receiving ATTENACE and patients receiving placebo were observed in all of the teacher, parent, and physician-rated scales beginning at week 1 and continuing throughout the study (Figure 1). Both inattention and hyperactivity/impulsivity subscale scores showed statistically significant improvements from baseline to endpoint for patients receiving ATTENACE compared to patients receiving placebo.

Table 1. ADHD Rating Scale IV (School Version)
Mean Change From Baseline to Final Visit

	<u>ATTENACE</u>		<u>Placebo</u>	
	<u>Baseline Score</u>	<u>Change from Baseline</u>	<u>Baseline Score</u>	<u>Change from Baseline</u>
<u>Study 1</u>	<u>38.6</u>	<u>-17.5*</u>	<u>37.8</u>	<u>-9.7</u>
<u>Study 2</u>	<u>35.7</u>	<u>-15.0.*</u>	<u>35.3</u>	<u>-7.3</u>
<u>Study 3</u>	<u>37.8</u>	<u>-17.2*</u>	<u>36.6</u>	<u>-8.2</u>
<u>Combined</u>	<u>37.2</u>	<u>-16.4*</u>	<u>36.5</u>	<u>-8.3</u>

*Significantly different than placebo (p<0.0001)

Figure 1. Change From Baseline to Each Time Point and to Endpoint for the Total Scores From the ADHD Rating Scale-IV (School Version) for Studies 1, 2, and 3



INDICATIONS AND USAGE

ATTENACE is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

The effectiveness of ATTENACE in the treatment of ADHD was established in 3 randomized, double-blind, placebo-controlled studies in children and adolescents (age 6 – 17 years) who met DSM-IV criteria for ADHD (See **CLINICAL TRIALS**).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and must be present in 2 or more settings, e.g., school (or work) and at

home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming, leaving seat, inappropriate running/climbing, difficulty with quiet activities, “on the go”, excessive talking, blurting answers, can’t wait turn, intrusive. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

Special Diagnostic Considerations

The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

ATTENACE is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in children and adolescents with this diagnosis and psychological intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment medication will depend upon the physician’s assessment of the chronicity and severity of the patient’s symptoms.

Long-Term Use

The effectiveness of ATTENACE for long-term use, i.e., for more than 9 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ATTENACE for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE and ADMINISTRATION**).

CONTRAINDICATIONS

ATTENACE is contraindicated in patients with known hypersensitivity to modafinil or its inactive ingredients.

WARNINGS

[Once you have provided additional information regarding the occurrence of serious rashes in association with the use of modafinil in pediatric patients, we ask that you propose a warning statement to alert health care providers to this risk. The patient information leaflet will also need to be updated regarding this risk of serious rash.]

Growth

As with other medications used to treat ADHD, growth should be monitored during treatment with ATTENACE. In the phase 3 double-blind studies, there was a 0.9 cm increase in height in both the ATTENACE- and placebo-treated patient groups. In the phase 3 open-label study (n=533), there was a 2.7 cm increase in height with no change in the height percentile (51).

In the phase 3 double-blind studies, the ATTENACE-treated patients lost on average 0.7 kg and placebo-treated patients gained on average 1.0 kg. In the phase 3 open-label study, patients treated with ATTENACE gained an average of 0.7 kg while mean weight percentile decreased slightly from 62 to 57.

In the placebo-controlled studies, 36 (9%) patients receiving ATTENACE and 3 (1%) patients receiving placebo, had a decrease of $\geq 7\%$ in body weight. For the majority of the patients, the magnitude of change in weight was relatively small compared with age and gender specific norms.

PRECAUTIONS

General

Although modafinil has not been shown to produce functional impairment, any drug affecting the CNS may alter judgment, thinking or motor skills. Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that ATTENACE therapy will not adversely affect their ability to engage in such activities.

Patients Using Contraceptives

The effectiveness of steroidal contraceptives may be reduced when used with ATTENACE tablets and for one month after discontinuation of therapy (See **Drug Interactions**). Alternative or concomitant methods of contraception are recommended for patients treated with ATTENACE tablets, and for one month after discontinuation of ATTENACE.

Cardiovascular System

In clinical studies of adults, signs and symptoms including chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG were observed in three subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that ATTENACE tablets not be used in patients with a history of left ventricular hypertrophy [or other underlying structural cardiac defects](#), or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. Such signs may include but are not limited to ischemic ECG changes, chest pain, or arrhythmia.

Central Nervous System

[\[This section will likely need to be expanded once you have responded to our request for additional information on psychiatric adverse events.\]](#)

There have been reports of psychotic episodes associated with modafinil use. One healthy adult male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of modafinil and sleep deprivation. There was no evidence of psychosis 36 hours after drug discontinuation. An eight year old patient with a prior history of psychosis and bipolar disorder experienced a psychotic episode. Caution should be exercised when ATTENACE is given to patients with a history of psychosis.

Patients with Severe Renal Impairment

In adult patients with severe renal impairment (mean creatinine clearance = 16.6 mL/min), a 200 mg single dose of modafinil did not lead to increased exposure to modafinil but resulted in much higher exposure to the inactive metabolite, modafinil acid, than is seen in subjects with normal renal function. There is little information available about the safety of such levels of this metabolite (See **CLINICAL PHARMACOLOGY**).

Patients with Severe Hepatic Impairment

In adult patients with severe hepatic impairment, with or without cirrhosis (See **CLINICAL PHARMACOLOGY**), ATTENACE should be administered at a reduced dose as the clearance of modafinil was decreased compared to that in normal subjects (See **DOSAGE and ADMINISTRATION**).

Information for Patients

Patients, parents or caregivers should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking ATTENACE. See Patient Information at the end of this labeling for the text of the leaflet provided for patients.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be cautioned regarding the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with ATTENACE and for one month after discontinuation of therapy (See *Impairment of Fertility* and **Pregnancy**).

Nursing

Patients should be advised to notify their physician if they are breast feeding an infant.

Concomitant Medication

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, because of the potential for interactions between ATTENACE and other drugs.

Alcohol

Patients should be advised that the use of ATTENACE in combination with alcohol has not been studied. Patients should be advised that it is prudent to avoid alcohol while taking ATTENACE.

Allergic Reactions

Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Drug Interactions

CNS Active Drugs

Methylphenidate - In a single-dose study in healthy adult volunteers, simultaneous administration of modafinil (200 mg) with methylphenidate (40 mg) did not cause any significant alterations in the pharmacokinetics of either drug. However, the absorption of modafinil may be delayed by approximately one hour when coadministered with methylphenidate.

Dextroamphetamine - In a single dose study in healthy adult volunteers, simultaneous administration of modafinil (200 mg) with dextroamphetamine (10 mg) did not cause any significant alterations in the pharmacokinetics of either drug. However, the absorption of modafinil may be delayed by approximately one hour when coadministered with dextroamphetamine.

Clomipramine - The coadministration of a single dose of clomipramine (50 mg) on the first of three days of treatment with modafinil (200 mg/day) in healthy adult volunteers did not show an effect on the pharmacokinetics of either drug. However, one incident of increased levels of clomipramine and its active metabolite desmethylclomipramine has been reported in a patient with narcolepsy during treatment with modafinil.

Triazolam – In the drug interaction study between modafinil and ethinyl estradiol (EE₂), on the same days as those for the plasma sampling for EE₂ pharmacokinetics, a single dose of triazolam (0.125 mg) was also administered. Mean C_{max} and AUC_{0-∞} of triazolam were decreased by 42% and 59%, respectively, and its elimination half-life was decreased by approximately an hour after the modafinil treatment.

Monoamine Oxidase (MAO) Inhibitors - Interaction studies with monoamine oxidase inhibitors have not been performed. Therefore, caution should be used when concomitantly administering MAO inhibitors and modafinil.

Other Drugs

Warfarin - There were no significant changes in the pharmacokinetic profiles of R- and S-warfarin in healthy adult subjects given a single dose of racemic warfarin (5 mg) following chronic administration of modafinil (200 mg/day for 7 days followed by 400 mg/day for 27 days) relative to the profiles in subjects given placebo. However, more frequent monitoring of prothrombin times/INR is advisable whenever ATTENACE is coadministered with warfarin (See **CLINICAL PHARMACOLOGY, Pharmacokinetics**, Drug-Drug Interactions).

Ethinyl Estradiol - Administration of modafinil to female adult volunteers once daily at 200 mg/day for 7 days followed by 400 mg/day for 21 days resulted in a mean 11% decrease in C_{max} and 18% decrease in AUC_{0-24} of ethinyl estradiol (EE₂; 0.035 mg; administered orally with norgestimate). There was no apparent change in the elimination rate of ethinyl estradiol.

Cyclosporine - One case of an interaction between modafinil and cyclosporine, a substrate of CYP3A4, has been reported in a 41 year old woman who had undergone an organ transplant. After one month of administration of 200 mg/day of modafinil, cyclosporine blood levels were decreased by 50%. The interaction was postulated to be due to the increased metabolism of cyclosporine, since no other factor expected to affect the disposition of the drug had changed. Dosage adjustment for cyclosporine may be needed.

Potential Interactions with Drugs That Inhibit, Induce, or are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes

In *in vitro* studies using primary human hepatocyte cultures, modafinil [and modafinil sulfone](#) ~~were~~ shown to [slightly](#) induce CYP1A2, CYP2B6 and CYP3A4 in a concentration-dependent manner. ~~In addition, modafinil sulfone induced at least CYP1A2. Although induction results based on in vitro experiments are not necessarily predictive of response in vivo~~ [In pediatric patients, concentrations of the modafinil sulfone metabolite are high and sustained. Induction may be more prominent in children due to their higher exposure to modafinil sulfone.](#) [Therefore](#), caution needs to be exercised when ATTENACE is coadministered with drugs that

depend on these three enzymes for their clearance ([e.g., theophylline](#)). Specifically, lower blood levels of such drugs could result (See *Other Drugs*, Cyclosporine above).

The exposure of human hepatocytes to modafinil *in vitro* produced an apparent concentration-related suppression of expression of CYP2C9 activity suggesting that there is a potential for a metabolic interaction between modafinil and the substrates of this enzyme (e.g., S-warfarin and phenytoin). However, a suppressive effect on CYP2C9 activity was not reproduced in a subsequent *in vitro* study, and in a clinical study in healthy adult volunteers, chronic modafinil treatment did not show a significant effect on the single-dose pharmacokinetics of warfarin when compared to placebo (See **PRECAUTIONS, Drug Interactions**, Warfarin).

In vitro studies using human liver microsomes showed that modafinil reversibly inhibited CYP2C19 at pharmacologically relevant concentrations of modafinil. CYP2C19 is also reversibly inhibited, with slightly higher potency, by a circulating metabolite, modafinil sulfone. In adults, sustained exposure to modafinil sulfone is observed, but at concentrations that are lower than those of the parent compound. In ~~some~~ pediatric patients, ~~however, sustained, high levels concentrations~~ of the sulfone metabolite are ~~higher than modafinil present~~, suggesting that a significant inhibitory effect on CYP2C19 activity may occur. Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin, omeprazole or S-mephenytoin may have prolonged elimination upon coadministration with ATTENACE and may require dosage reduction and monitoring for toxicity.

Tricyclic antidepressants - CYP2C19 also provides an ancillary pathway for the metabolism of certain tricyclic antidepressants (e.g., clomipramine, atomoxetine and desipramine) that are primarily metabolized by CYP2D6. In tricyclic-treated patients deficient in CYP2D6 (i.e., those who are poor metabolizers of debrisoquine; 7-10% of the Caucasian population; similar or lower in other populations), the fraction of metabolic elimination that proceeds via CYP2C19 may be substantially increased. ATTENACE may cause elevation of the levels of the tricyclics in this subset of patients. Physicians should be aware that a reduction in the dose of tricyclic agents might be needed in these patients.

In addition, due to the partial involvement of CYP3A4 in the metabolic elimination of modafinil, coadministration of potent inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin)

or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) could alter the plasma levels of modafinil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

[The following were used to calculate the animal-to-human mg/m² ratios:

-Maximum recommended human mg/kg dose: 425 mg/30 kg = 14.2 (for comparison with carcinogenicity and juvenile studies) or 425 mg/40 kg = 10.6 (reproduction studies).

-Mg/kg-to-mg/m² conversion factor for humans = 28 (carcinogenicity and juvenile studies) or 31 (reproduction studies).

-Mg/kg-to mg/m² conversion factors for mouse, rat, and rabbit = 3, 6, and 12, respectively].

Carcinogenesis

Carcinogenicity studies were conducted in which modafinil was administered in the diet to mice for 78 weeks and to rats for 104 weeks at doses of 6, 30 and 60 mg/kg/day. The highest dose studied is 0.5 times (mouse) or the same as (rat) the maximum recommended human daily dose of 425 mg on a mg/m² basis. ~~The highest dose studied represents 0.45 times (mouse) or 0.9 times (rat) greater than the recommended daily dose of 425 mg on a mg/m² basis.~~ There was no evidence of tumorigenesis associated with modafinil administration in these studies, but because the mouse study used an inadequate high dose that was not representative of a maximum tolerated dose, the carcinogenic potential of modafinil has not been fully evaluated.

Mutagenesis

There was no evidence of mutagenic or clastogenic potential of modafinil in a series of assays. It was not mutagenic in the *in vitro* Ames bacterial reverse mutation test, the *in vitro* mouse lymphoma/TK locus assay in the presence or absence of metabolic activation; and it was not clastogenic in the *in vitro* human lymphocyte chromosomal aberration assay in the presence or absence of metabolic activation, or in two *in vivo* mouse bone marrow micronucleus assays. Modafinil did not increase unscheduled DNA synthesis in rat hepatocytes. In a cell transformation assay in BALB/3T3 mouse embryo cells, modafinil did not cause an increase in the frequency of transformed foci in the presence or absence of metabolic activation.

Impairment of Fertility

Oral administration of modafinil to male and female rats had no effects on fertility when administered prior to and throughout mating, and continued in females through day 7 of gestation, at doses up to 480 mg/kg/day (9 times the maximum recommended human daily dose of 425 mg on a mg/m² basis). (~~7 times the recommended daily dose of 425 mg/day on a mg/m² basis~~).

Pregnancy

Pregnancy Category C: Modafinil administered orally to pregnant rats throughout the period of organogenesis caused, in the absence of maternal toxicity, an increase in resorptions and an increased incidence of hydronephrosis and skeletal variations in the offspring at a dose of 200 mg/kg/day (4 times the maximum recommended human daily dose of 425 mg on a mg/m² basis) (~~3 times the recommended daily dose of 425 mg/day on a mg/m² basis~~), but not at 100 mg/kg/day. However, in a subsequent study of up to 480 mg/kg/day (9 times the maximum recommended human daily dose on a mg/m² basis) (~~7 times the recommended daily dose on a mg/m² basis~~), which included maternally toxic doses, no adverse effects on embryofetal development were seen.

Modafinil administered orally to pregnant rabbits throughout the period of organogenesis at doses up to 100 mg/kg/day (4 times the maximum recommended human daily dose on a mg/m² basis) (~~3 times the recommended daily dose on a mg/m² basis~~) had no effects on embryofetal development.

However, in a subsequent study in pregnant rabbits, increased resorptions, and increased alterations in fetuses from a single litter (open eye lids, fused digits, rotated limbs), were observed at 180 mg/kg/day (7 times the maximum recommended human daily dose on a mg/m² basis) (~~5.4 times the recommended daily dose on a mg/m² basis~~), a dose that was also maternally toxic.

Modafinil administered orally to rats throughout gestation and lactation at doses up to 200 mg/kg/day (4 times the maximum recommended human daily dose on a mg/m² basis) (~~3 times the~~

~~recommended daily dose on a mg/m² basis~~), had no effects on the postnatal development of the offspring.

There are no adequate and well-controlled studies in pregnant women. Modafinil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of modafinil on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received modafinil during pregnancy. One patient gave birth 3 weeks earlier than the expected range of delivery dates (estimated using ultrasound) to a healthy male infant. One woman with a history of spontaneous abortions suffered a spontaneous abortion while being treated with modafinil.

Nursing Mothers

It is not known whether modafinil or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ATTENACE tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ATTENACE in individuals below 6 years of age have not been established.

A 13-week study was conducted in young rats to evaluate the effects of ATTENACE on skeletal growth, sexual development, and neurobehavioral development. Rat pups were treated with 30, 120 or 240 mg/kg/day (0.5, to 4 times the maximum [human](#) daily dose [of 425 mg](#) on a mg/m² basis [~~Note: based on a dose of 425 mg and a body weight of 30 kg~~]) of modafinil via oral gavage beginning on Day 10 *post partum* and continuing through adulthood. No effect on skeletal growth as assessed by femur length measurements was observed at completion of the dosing period. Sexual maturation (vaginal patency, preputial separation, estrus cycling, sperm counts, and mating performance) were not affected. A slight decrease in motor activity was noted on Days 23 (≥ 30 mg/kg/day) and Days 96-99 (≥ 120 mg/kg/day) *post partum*; [this was not seen after a 4 week recovery period](#). ~~Female rat pups tended to be more easily removed from their home cage on Day 23 *post partum* (≥ 30 mg/kg/day).~~ There were no effects on learning and

memory tests. ~~Partial or full reversibility of effects was observed at completion of a 4-week recovery period.~~ The significance of these findings to humans is unknown.

Geriatric Use

Safety and effectiveness in individuals above 65 years of age have not been established.

ADVERSE REACTIONS

Modafinil was administered to 933 children or adolescent patients with ADHD in clinical studies. ~~In clinical trials, modafinil has been found to be generally well-tolerated and most adverse experiences were mild to moderate.~~

The most commonly observed adverse events ($\geq 5\%$) associated with the use of ATTENACE more frequently than placebo-treated patients in the placebo-controlled clinical studies were insomnia, headache, anorexia (decreased appetite), abdominal pain, fever, and nervousness. The adverse event profile was similar across these studies.

In the phase 3, placebo-controlled clinical trials, 5% (21 of 420) of the patients who received ATTENACE discontinued due to an adverse experience compared to 3% (7 of 213) of patients who received placebo. The most frequent reasons for discontinuation were insomnia (1%, n=5), abdominal pain (<1%, n=3), and emotional lability (<1%, n=3).

Incidence in Controlled Trials

The following table presents the adverse experiences that occurred at a rate of 2% or more and were more frequent in patients treated with ATTENACE than in placebo patients in the principal, placebo-controlled clinical trials.

The prescriber should be aware that the figures provided below cannot be used to predict the frequency of adverse experiences in the course of usual medical practice, where patient characteristics and other factors may differ from those occurring during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. Review of these

frequencies, however, provides prescribers with a basis to estimate the relative contribution of drug and non-drug factors to the incidence of adverse events in the population studied.

Table 2. Incidence of Treatment-Emergent Adverse Experiences In Parallel-Group, Placebo-Controlled Clinical Trials with ATTENACE¹

Body System	Preferred Term	Modafinil (n = 420)	Placebo (n = 213)
Body as a Whole	Headache	20%	13%
	Abdominal Pain	10%	8%
	Fever	5%	3%
	Pain	3%	2%
Digestive	Anorexia	16%	3%
	Nausea	4%	2%
	Dry Mouth	2%	1%
	Dyspepsia	2%	1%
	Gastroenteritis	2%	1%
Hemic/Lymphatic	Ecchymosis	2%	0%
Metabolic/Nutritional	Weight Loss	4%	1%
Nervous	Insomnia	27%	4%
	Nervousness	5%	4%
	Dizziness	2%	1%
Skin/Appendages	Rash	4%	2%

¹ Events reported in the three double-blind placebo controlled clinical studies by at least 2% of patients treated with ATTENACE that were more frequent than in the placebo group are included; incidence is rounded to the nearest 1%. The adverse experience terminology is coded using a standard modified COSTART Dictionary.

Events for which the ATTENACE incidence was 1%, but greater than placebo are not listed in the table. These events include: twitching, depression, tremor, and pruritus.

Events for which the ATTENACE incidence was at least 1%, but equal to or less than placebo are not listed in the table. These events included the following: infection, accidental injury, flu syndrome, bacterial infection, allergic reaction, viral infection, tachycardia, vomiting, diarrhea, emotional lability, somnolence, agitation, anxiety, hostility, increased cough, rhinitis, pharyngitis, sinusitis,

[We have deleted the language suggesting a decline in insomnia and anorexia over time. These trials were not designed to accurately assess changes in adverse events over time, and the accumulated data are difficult to interpret. Many patient dropped out for the very events being assessed. In addition, patients and raters may be less inclined to report an event that continues to occur, unless specifically prompted.]

Insomnia and Anorexia (decreased appetite)

~~In the phase 3 studies, the incidence of these adverse events decreased substantially from the first 2 weeks of double-blind treatment to the second 2 weeks of treatment. Among patients treated with ATTENACE, the incidence of insomnia and anorexia decreased from 20% and 10% respectively during the first 2 weeks, to 8% and 6% respectively during weeks 2 to 4 of which a total of 7 patients discontinued treatment because of insomnia (n=5), or anorexia (n=2).~~

Vital Sign Changes

In the Phase 3 studies, there were no differences between the ATTENACE and placebo treatment groups with respect to changes in vital signs; including heart rate, systolic and diastolic blood pressure, and body temperature.

Weight Changes

In the phase 3 double-blind studies, the ATTENACE-treated patients had on average a 0.7 kg decrease in weight and placebo-treated patients had on average a 1.0 kg increase. In the phase 3 open-label study, patients treated with ATTENACE had on average an increase of 0.7 kg while mean weight percentile decreased slightly from 62 to 57 (See **WARNINGS**).

Laboratory Changes

Hematology

In phase 3, placebo-controlled studies, there were no marked differences between the ATTENACE and placebo treatment groups in the incidence of clinically significantly abnormal hematology values. Low ANC values ($\leq 1 \times 10^9/L$) were seen in 2% patients in both the ATTENACE treatment group and in the placebo treatment group. Low WBC values ($\leq 3 \times 10^9/L$) were seen in 2% of the ATTENACE-treated patients and in 1% placebo-treated patients. The majority of the patients with clinically significantly abnormal ANC and/or WBC values also had corresponding elevations in the lymphocytes and/or monocytes, suggesting the presence of a viral syndrome in these patients.

Blood Chemistry

In the phase 3 placebo-controlled studies, the only notable differences between the ATTENACE and placebo treatment groups were a mean decrease in uric acid (19.4 $\mu\text{mol/L}$) and mean increases in alkaline phosphatase (16.8 units/L) and GGT (6.3 units/L). Even with these changes, most values remained within normal range. The effect of ATTENACE on alkaline phosphatase and GGT appear to be more pronounced in the higher dosage groups (340 and 425mg/day), and were not accompanied by increases in ALT, AST, or total bilirubin. Elevations of alkaline phosphatase and GGT have previously been observed in adults.

ECG Changes

In the phase 3, placebo-controlled studies, there were no differences between the ATTENACE and placebo treatment groups with respect to ECG interval durations, including QTc.

Postmarketing Reports

The following adverse reactions have been identified during post-approval use of modafinil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to modafinil.

Central Nervous System: symptoms of psychosis, symptoms of mania

Dermatologic: rare reports of serious skin reactions (including suspected cases of both erythema multiforme and Stevens-Johnson syndrome)

Hematologic: agranulocytosis

Hypersensitivity: urticaria (hives), angioedema

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Modafinil (ATTENACE) is listed in Schedule IV of the Controlled Substances Act.

Abuse Potential and Dependence

In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. In *in vitro* binding studies, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies, modafinil was also partially discriminated as stimulant-like. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (e.g., methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (e.g., incrementation of doses or drug-seeking behavior).

The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to methylphenidate (45 and 90 mg) in an inpatient study in individuals experienced with drugs of

abuse. Results from this clinical study demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate).

Withdrawal

The abrupt withdrawal from ATTENACE treatment did not have any effect on physical or emotional health of the patients as assessed by the STESS (Subject's Treatment Emergent Symptom Scale). In addition, there was no evidence of symptom rebound or adverse events suggesting a drug-discontinuation or withdrawal syndrome.

OVERDOSAGE

Human Experience

In clinical trials, a total of 151 protocol-specified doses ranging from 1000 to 1600 mg/day (more than 2 times the recommended daily dose of 425 mg) have been administered to 32 subjects, including 13 subjects who received doses of 1000 or 1200 mg/day for 7 to 21 consecutive days. In addition, several intentional acute overdoses occurred; the two largest being 4500 mg and 4000 mg taken by two subjects participating in foreign depression studies. None of these study subjects experienced any unexpected or life-threatening effects. Adverse experiences that were reported at these doses included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea and decreased prothrombin time.

From post-marketing experience, there have been no reports of fatal overdoses involving modafinil alone (doses up to 12 grams). Overdoses involving multiple drugs, including modafinil, have resulted in fatal outcomes. Symptoms most often accompanying modafinil overdose, alone or in combination with other drugs have included: insomnia; central nervous system symptoms such as restlessness, disorientation, confusion, excitation and hallucination; digestive changes such as nausea and diarrhea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain.

Cases of accidental ingestion/overdose have been reported in children as young as 11 months of age. The highest reported accidental ingestion on a mg/kg basis occurred in a three-year-old boy

who ingested 800-1000 mg (50-63 mg/kg) of modafinil. The child remained stable. The symptoms associated with overdose in children were similar to those observed in adults.

Overdose Management

No specific antidote to the toxic effects of modafinil overdose has been identified to date. Such overdoses should be managed with primarily supportive care, including cardiovascular monitoring. If there are no contraindications, induced emesis or gastric lavage should be considered. There are no data to suggest the utility of dialysis or urinary acidification or alkalization in enhancing drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.

DOSAGE and ADMINISTRATION

Initial Treatment

ATTENACE should be taken as a single dose, in the morning, with or without food. Dosage should be individualized according to the needs and responses of the patient. In clinical trials, treatment was initiated at 85 mg /day. The daily dosage was increased by 85 mg increments every 2 to 7 days until the optimum or target daily dose was achieved. Doses above 425 mg have not been systematically evaluated. (See **CLINICAL TRIALS**).

The following target daily doses of ATTENACE are recommended:

Patients less than 30 kg of body weight: 340 mg

Patients at least 30 kg of body weight: 425 mg

Maintenance/Extended Treatment

There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with ATTENACE. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use ATTENACE for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Dosage adjustment should be considered for concomitant medications that are substrates for CYP3A4, such as triazolam and cyclosporine (See **PRECAUTIONS, Drug Interactions**).

Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin (also via CYP2C9) or S-mephenytoin may have prolonged elimination upon coadministration with ATTENACE and may require dosage reduction and monitoring for toxicity.

In patients with severe hepatic impairment, the dose of ATTENACE should be reduced to one-half of that recommended for patients with normal hepatic function (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

HOW SUPPLIED:

ATTENACE (modafinil) Tablets

- 85 mg** Each capsule-shaped, white, film-coated tablet is debossed with the Cephalon "C" logo on one side and "111" on the other.
NDC 63459-111-60 - Bottles of 60
NDC 63459-111-01 - Bottles of 100
- 170 mg** Each capsule-shaped, light yellow, film-coated tablet is debossed with the Cephalon "C" logo on one side and "112" on the other.
NDC 63459-112-60 - Bottles of 60
NDC 63459-112-01 - Bottles of 100
- 255 mg** Each capsule-shaped, light blue, film-coated tablet is debossed with the Cephalon "C" logo on one side and "113" on the other.
NDC 63459-113-30 - Bottles of 30
NDC 63459-113-01 - Bottles of 100
- 340 mg** Each capsule-shaped, dark yellow, film-coated tablet is debossed with the Cephalon "C" logo on one side and "114" on the other.
NDC 63459-114-30 - Bottles of 30
NDC 63459-114-01 - Bottles of 100
- 425 mg** Each capsule-shaped, dark blue, film-coated tablet is debossed with the Cephalon "C" logo on one side and "115" on the other.
NDC 63459-115-30 - Bottles of 30
NDC 63459-115-01 - Bottles of 100

Store at 20° - 25° C (68° - 77° F).

Manufactured for:

Cephalon, Inc.
West Chester, PA 19380

U.S. Patent Nos. RE37,516 / 6,346,548

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ATTEN-xxx

INFORMATION FOR PATIENTS OR THEIR PARENTS OR CAREGIVERS
ATTENACE (Ah-TEN-ace) Tablets [C-IV]
Generic name: modafinil

Read the Patient Information that comes with ATTENACE before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

What is ATTENACE?

ATTENACE is a medicine to treat Attention-Deficit/Hyperactivity Disorder (ADHD). ATTENACE contains modafinil. Your doctor has prescribed this medicine as part of an overall treatment plan to control your symptoms of ADHD.

ATTENACE is a controlled substance [C-IV]. This means that ATTENACE may be a target for people who abuse medicines or street drugs. Keep your ATTENACE in a safe place. Giving away ATTENACE is against the law.

What is ADHD?

ADHD has 3 main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all 3 types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

Who should NOT take ATTENACE?

Do not take ATTENACE if you are allergic to any of its ingredients. The active ingredient is modafinil. See the end of this leaflet for a complete list of ingredients.

Do not take ATTENACE if you are already taking PROVIGIL[®] Tablets, or any other medicines that contain modafinil.

Before starting ATTENACE tell your doctor

- about all your medical conditions, including if you:
 - are pregnant, are planning to become pregnant, or are breastfeeding. It is not known if ATTENACE may harm your unborn baby, or if ATTENACE passes into your milk and if it can harm your baby.
 - have high blood pressure or heart problems.
 - have liver or kidney problems.
 - have abused medicines called “stimulants” or street drugs.
 - have or had a mental problem called psychosis.

- about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ATTENACE and many other medicines can interact with each other causing side effects. ATTENACE may affect the way other medicines work, and other medicines may affect how ATTENACE works. Keep a list of all medicines you take. Your doctor or pharmacist will tell you if it is safe to take ATTENACE and other medicines together. Do not take other medicines with ATTENACE unless your doctor has told you it is okay.

ATTENACE can affect hormonal birth control methods (contraceptives). Women who use hormonal contraceptives such as birth control pills, shots, implants, intrauterine devices (IUDs) or patches, may have a higher chance for getting pregnant while taking ATTENACE, and for one month after stopping ATTENACE. Talk to your doctor about birth control methods that are right for you while using ATTENACE.

How should I take ATTENACE?

- Take ATTENACE exactly as prescribed by your doctor. Your doctor will prescribe the dose of ATTENACE that is right for you. Do not change your dose of ATTENACE without talking to your doctor. Do not take more ATTENACE than prescribed.
- You can take ATTENACE with or without food.
- You should take ATTENACE once each day in the morning.
- If you take more than your prescribed dose, or take ATTENACE too late in the day, you may find it harder to go to sleep. Call your doctor if you have any concerns.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What should I avoid while taking ATTENACE?

- Do not take other medicines including prescription and non-prescription medicines, vitamins or herbal supplements unless your doctor has told you it is okay.
- You should avoid drinking alcohol.

What are the possible side effects of ATTENACE?

The most common side effects of ATTENACE are insomnia, headache, decreased appetite, abdominal pain, fever, and nervousness.

ATTENACE may cause the following infrequent serious side effects. Call your doctor or get emergency help if you have any of these or any other serious side effects while taking ATTENACE:

- mental problems
- allergic reactions, such as a rash, hives or other allergic reaction

Some effects of ATTENACE on the brain are similar to other medications called “stimulants”. If you have a history of drug and/or stimulant use or abuse you should discuss this with your doctor before starting ATTENACE.

Tell your doctor if you get any side effects while taking ATTENACE.

These are not all the side effects of ATTENACE. For more information, ask your doctor or pharmacist.

How should I store ATTENACE?

- Store ATTENACE at room temperature, 68° to 77° F (20° to 25° C).
- Store ATTENACE in a safe place.
- Keep ATTENACE and all medicines out of the reach of children.

General information about ATTENACE

Medicines are sometimes prescribed for conditions that are not listed in patient information leaflets. Do not use ATTENACE for a condition for which it is not prescribed. This medication is for your use only. Do not share this medication with others.

This leaflet summarizes the most important information about ATTENACE. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ATTENACE that is written for health professionals. For more information, please call 1-800-896-5855, or go to www.ATTENACE.com.

What are the ingredients in ATTENACE?

Active Ingredient: modafinil

Inactive Ingredients: lactose, croscarmellose sodium, povidone, and non-bovine magnesium stearate. The coating on the outside of the tablet contains: hypromellose, titanium dioxide, lactose, polyethylene glycol, and triacetin. Some tablet coatings also contain: iron oxide yellow or FD&C Blue #2.

Rx Only

Month 200X

Cephalon, Inc. West Chester, PA 19380.

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this page is the manifestation of the electronic signature.**

/s/

Thomas Laughren
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