ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2009; 29 (9): 613-623
1173-2563/09/0009-0613/$49.95/0

Armodafinil and Modafinil Have Substantially Different Pharmacokinetic Profiles Despite Having the Same Terminal Half-Lives

Analysis of Data from Three Randomized, Single-Dose, Pharmacokinetic Studies

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Abstract

Background and objective: Armodafinil, a non-amphetamine, wakefulness-promoting medication, is the *R*- and longer-lasting isomer of racemic modafinil. Armodafinil has been shown to improve wakefulness in patients with excessive sleepiness (ES) associated with treated obstructive sleep apnoea, shift work disorder or narcolepsy. In comparison with modafinil, armodafinil maintains higher plasma concentrations later in the day in healthy subjects. The objective of this analysis was to characterize the pharmacokinetic parameters related to those higher concentrations.

Methods: Data from three randomized studies in healthy adult subjects receiving single doses of either armodafinil (50, 100, 200, 250, 300 or 400 mg) or modafinil (400 mg) were pooled, and subsequently dose-normalized to a 200 mg dose for each drug. Non-compartmental pharmacokinetic parameters were assessed.

Results: Armodafinil and modafinil both had a mean single-dose terminal elimination half-life of ~13 hours, with similar mean maximum plasma drug concentration (C_{max}) and median time to C_{max} values. After reaching C_{max}, plasma concentrations appeared to decline in a monophasic manner with armodafinil, but in a biphasic manner with modafinil due to the initial rapid elimination of its *S*-isomer. As a result, mean area under the plasma drug concentration versus time curve (AUC) from time zero to the time of the last measurable concentration (AUC_{last}) and AUC from time zero to infinity (AUC_{∞}) values were 33% and 40% higher, respectively, with armodafinil compared with modafinil on a milligram-to-milligram basis.

Conclusions: Despite similar half-lives, plasma concentrations following armodafinil administration are higher late in the day than those following modafinil administration on a milligram-to-milligram basis. The different pharmacokinetic profile of armodafinil may result in improved wakefulness throughout the day in patients with ES compared with modafinil.

Background

Armodafinil is the *R*- and longer-lasting isomer of racemic modafinil. Armodafinil is a non-amphetamine, wakefulness-promoting medication that has been shown to significantly improve excessive sleepiness (ES) associated with treated obstructive sleep apnoea (OSA),[1,2] shift work disorder[3] or narcolepsy.[4] Modafinil and its *R*- and *S*-isomers demonstrate similar inhibition of binding and functional activity at dopamine, norepinephrine and serotonin transporters as measured by *in vitro* pharmacological activity assessments.[5] While the *S*-isomer, which accounts for one-half of racemic modafinil, demonstrates equivalent pharmacological activity to the *R*-isomer, the isomers exhibit different pharmacokinetic profiles. The *S*-isomer has a relatively short terminal elimination half-life ($t_{½\beta}$) [4–5 hours] compared with that of the *R*-isomer, which is approximately 3–4 times longer (~15 hours).[6,7]

Despite this stereospecific difference in elimination of the two isomers, pharmacokinetic studies of armodafinil and modafinil administered in single and multiple doses to healthy subjects have generally demonstrated that the two drugs have identical $t_{½\beta}$ values in the range of 12–16 hours.[6-9] However, consideration of the $t_{½\beta}$ value alone does not give an indication of the plasma concentration profiles of the two drugs over an entire dosing interval (especially late in the afternoon and early evening), the degree of fluctuation or swing in plasma concentrations over a dosing interval, or the systemic availability of the two drugs when administered at similar dosages.

A recent pharmacokinetic analysis[10] compared the steady-state plasma concentration profiles of armodafinil and modafinil achieved with similar daily dosages administered over a period of 7 days to healthy subjects. The average, late-day plasma concentration over the time interval from 3pm–7pm, or 7–11 hours after dosing [$C_{avg(7–11)}$], was 43% higher with armodafinil compared with modafinil. Plasma armodafinil concentration fluctuation and swing were 28% and 42% less, respectively, over the 24-hour dosing interval.

The wakefulness-promoting effects of racemic modafinil are not always maintained throughout the day with once-daily dosing of 200 mg. Some patients may require higher doses (400 mg) or dose-splitting (400 mg or 600 mg split dose) of modafinil to effectively alleviate ES later in the day, potentially increasing the risk of adverse effects and/or necessitating inconvenient dosing regimens.[11-13] Armodafinil has shown the potential to maintain a pharmacodynamic effect late in the day compared with similar doses of modafinil. Data in healthy subjects who underwent acute sleep deprivation suggest that a single dose of armodafinil 200 mg may increase the ability to sustain wakefulness and attention later in the dosing interval compared with the same dose of modafinil.[14] As was seen in the pharmacokinetic studies, despite similar peak concentrations at the same dosage, armodafinil produced significantly higher concentrations 6–14 hours after administration compared with modafinil.[14] The plasma concentration versus time profiles of the two drugs are consistent with the pharmacodynamic data.

The present analysis was undertaken to further investigate differences in the pharmacokinetic profiles of armodafinil and modafinil when administered at equal doses and to identify pharmacokinetic parameters responsible for differences in late-day plasma concentrations. Data were pooled from two randomized, single-dose pharmacokinetic studies of armodafinil in healthy subjects and compared with data from a similarly designed study with modafinil. Data from the two armodafinil studies have previously been presented as part of a wider analysis of three separate pharmacokinetic investigations in healthy subjects,[9] but the findings of the modafinil study have not previously been published.

Subjects and Methods

Study Designs

Studies 1 and 2, the pharmacokinetic studies of armodafinil, were conducted in the UK in 2003 and the US in 2004, respectively. Study 1 was a randomized, double-blind, placebo-controlled investigation

in which single doses of armodafinil 50 mg increasing sequentially to 400 mg were administered to healthy young men. Study 2 was a randomized, open-label, crossover investigation in healthy young men and women designed to establish the bioequivalence of a single dose of armodafinil administered as 1×250 mg uncoated tablet and an equivalent dose administered as 5×50 mg coated tablets. Study 3, which was conducted in the US in 1999, was a randomized, open-label, crossover investigation designed to establish the bioequivalence of two different tablet formulations of modafinil, both administered as a single dose of 400 mg (i.e. as 2×200 mg tablets).

As the three studies were single-dose pharmacokinetic investigations conducted in subjects with similar demographic characteristics selected via similar inclusion/exclusion criteria, *post hoc* comparison of the pharmacokinetic data derived from these studies was considered acceptable. Each study was approved by the Independent Ethics Committees/Institutional Review Boards at the respective study sites, and each was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines[15] and applicable national and local laws. Before any study-related procedures or assessments were performed, written informed consent was obtained from all participating subjects.

Subjects

Study 1 was conducted in men aged 22–39 years and study 2 in men or women aged 18–44 years who were in good health and had a body mass index of $\leq 30\ kg/m^2$. Exclusion criteria were similar in the two studies and included clinically significant, uncontrolled medical conditions; clinically significant abnormal laboratory values, vital signs, ECG or physical examination findings; a history of smoking or alcohol (ethanol) or drug abuse over the previous 2 years, or excessive consumption of caffeine-containing beverages; positive test results for hepatitis B surface antigen or hepatitis C antibodies; and HIV positive status. For study 2, female participants were required to be surgically sterile, 2 years postmenopausal, or using a medically accepted method of birth control if they could have children.

Study 3 with modafinil was conducted in men aged 21–45 years who were in good health and within 15% of their ideal bodyweight range for height (according to Metropolitan Life Insurance Company data for 1983). Exclusion criteria were similar to those applied in the two armodafinil studies.

Study Drugs

Subjects enrolled in study 1 were grouped into five panels and randomized in a double-blind fashion to receive single doses of 50 mg, 100 mg, 200 mg, 300 mg or 400 mg of armodafinil or matching placebo capsules in the morning (between 7am and 8am) after an overnight fast. Within each dose group, randomization was performed on a 3 : 1 (armodafinil : placebo) basis, and was achieved via a specific randomization code. The doses of armodafinil were studied sequentially in order to allow time to review the suitability of subsequent dose strengths planned. Each dose was given approximately 7 days after initiation of the previous dose. Subjects in the 100 mg dose panel returned 1 week later and received a second 100 mg dose after eating a standard fatty breakfast.

Subjects enrolled in the crossover, bioequivalence study of armodafinil tablet formulations (study 2) were randomized (1 : 1) in a non-blinded fashion to receive a single dose of 250 mg administered as either 5×50 mg coated tablets or 1×250 mg uncoated tablet in the morning (between 7:30am and 8:30am) after an overnight fast. Following a washout period of at least 7 days, the alternative regimen was administered, again in the morning after an overnight fast. Similarly, in study 3, subjects were randomized (1 : 1) in a non-blinded fashion to receive a single dose of modafinil 400 mg administered as either 2×200 mg original formulation tablets (formulation A) or 2×200 mg test formulation tablets (formulation B), both of which were given in the morning (between 7am and 10am) after an overnight fast. Following a washout period of at least 7 days, subjects received the same dose

(400 mg) given as the alternative formulation, again after an overnight fast.

Subjects participating in any of the three studies were not permitted to take any other prescription or over-the-counter medications (with the exception of paracetamol [acetaminophen] or ibuprofen in studies 1 and 2) during the investigations or within 2–4 weeks before administration of the study drugs. In addition, alcohol, antiseptic mouthwashes and grapefruit juice were not allowed 48 hours before drug administration or during sampling in studies 1 and 2.

Pharmacokinetic Assessments

Blood samples for detection of plasma concentrations were collected before armodafinil or modafinil administration on day 1 of each study and at pre-specified times after administration. In studies 1 and 2 (armodafinil), samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 13, 16, 24, 36, 48 and 72 hours after drug administration; in study 1, samples were also collected at 96 hours, and in study 2, at 60 hours. In study 2, samples were collected at the same times following the alternative dose regimen administered after the washout period of ≥7 days. In study 3 (modafinil), samples were collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24, 36, 48, 60 and 72 hours after each drug administration.

Plasma samples from studies 1 and 2 were analysed for concentrations of armodafinil (and its two primary circulating metabolites, *R*-modafinil acid and modafinil sulfone) by the Department of Drug Safety and Disposition of Cephalon, Inc., West Chester, PA, USA (study 1), or PPD Development, Middleton, WI, USA (study 2), using a validated high-performance liquid chromatography (HPLC) method with UV detection (see Darwish et al.[9] for details of the assay methodology). In study 3, plasma samples were analysed for concentrations of modafinil (and its two primary circulating metabolites modafinil acid and modafinil sulfone) by the Department of Drug Safety and Disposition, Cephalon, Inc., West Chester, PA, USA, using a validated HPLC method (see Wong et al.[6] for details of the assay methodology). For this analysis, pharmacokinetic data from subjects in study 1 who received armodafinil doses of 100 mg after a standard fatty meal were excluded because of a known food effect.[9] For studies 2 and 3, since bioequivalence was demonstrated, plasma drug concentrations achieved with the two tablet formulations were averaged for each subject at each time point.

Noncompartmental pharmacokinetic analysis was performed for all three studies. Standard pharmacokinetic parameters were determined using WinNonlin® (Enterprise versions 4.0.1 or 4.1 [studies 1 and 2] or Standard Edition version 1.1 [study 3], Pharsight Corporation, Mountain View, CA, USA). From individual plasma drug concentration data in the three studies, the following pharmacokinetic parameters of the two drugs were determined: maximum plasma concentration (C_{max}); time to reach C_{max} (t_{max}); area under the plasma concentration versus time curve (AUC) from time zero to the time of the last measurable concentration (AUC_{last}); AUC from time zero to infinity (AUC_{∞}); apparent terminal elimination rate constant (λ_z); and $t_{½\beta}$.

Because both armodafinil and modafinil have been reported to exhibit dose-proportional pharmacokinetics,[6,9] a dose-normalization procedure was considered justified. Plasma drug concentration and pharmacokinetic data for each subject were therefore normalized to a 200 mg dose.

Tolerability/Safety Assessments

The tolerability of the study medications was assessed by observing the subjects and asking non-leading questions about the occurrence of adverse events during the studies, and by monitoring clinical laboratory test results, vital signs, ECGs and physical examination findings at baseline and at specified times during the studies. Adverse events were classified according to the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) in studies 1 and 3, and the Medical Dictionary for Regulatory Activities (MedDRA) in study 2.

Statistical Analyses

Dose-normalization of plasma drug concentrations of the two drugs was performed by multiplying

Table I. Demographic characteristics of healthy subjects randomized to armodafinil or modafinil in the three studies[a]

Characteristic	Armodafinil studies[b] (N = 60)	Modafinil study (N = 24)	p-Value
Age (y)	29.0 ± 7.29	30.7 ± 7.05	0.3520[c]
Sex [n (%)]			
male	48 (80)	24 (100)	0.0180[d]
female	12 (20)	0	
Ethnicity [n (%)]			
White	39 (65)	18 (75)	0.0003[e]
Black	4 (7)	2 (8)	
Asian	0	1 (4)	
American Indian or Alaskan Native	0	3 (13)	
Hispanic	17 (28)	0	
Weight (kg)	76.4 ± 10.78	77.0 ± 10.73	0.8437[c]
Height (cm)	174.2 ± 9.25	178.2 ± 7.67	0.0645[c]
Body mass index (kg/m^2)	25.2 ± 2.83	24.3 ± 3.35	0.2213[c]

a Values are given as mean ± SD unless specified otherwise.

b Combined demographic data for subjects participating in the randomized, single-dose, placebo-controlled study (study 1) and the randomized, single-dose, crossover study (study 2) of armodafinil (excluding data for subjects randomized to placebo; n = 10).

c p-Value for the treatment comparison is from an ANOVA with treatment group as a factor.

d p-Value for the treatment comparison is from Pearson's chi-squared (χ^2) test.

e p-Value for the treatment comparison is from Fisher's exact test.

the individual subject data by the appropriate dose-normalization factor (i.e. 4 for the 50 mg dose, 2 for the 100 mg dose, 0.8 for the 250 mg dose, 0.67 for the 300 mg dose and 0.5 for the 400 mg doses), and then calculating the mean for each. All pharmacokinetic variables, except t_{max}, for which median was used, were summarized using mean ± standard deviation (SD) values for armodafinil or modafinil from the corresponding pooled, dose-normalized data. A 90% confidence interval (CI) was constructed for the geometric mean ratios between the two drugs.

Results

A total of 70 subjects were randomized in the two armodafinil studies (studies 1 and 2), and 24 subjects in the modafinil study (study 3) [table I]. In study 1, six subjects each received armodafinil doses of 50 mg, 100 mg, 200 mg, 300 mg or 400 mg, and ten subjects received placebo. In study 2, 30 subjects were randomized to armodafinil: 28 subjects received 250 mg as a single dose of 5 × 50 mg tablets, while 29 received 250 mg as a single dose of 1 × 250 mg tablet. Three subjects discontinued the study for reasons unrelated to the medication (two for personal reasons and one because of an anterior cruciate ligament tear and torn meniscus of the left knee). Pharmacokinetic data for another two subjects were excluded from this analysis because of apparent quantifiable concentrations of armodafinil prior to drug administration. Thus, the numbers of subjects evaluable for determination of pharmacokinetic parameters were 30 in study 1 and 25 in study 2. Because the two tablet formulations administered in study 2 met the requirements for bioequivalence in terms of 90% CIs in the range of 0.8–1.25 for the geometric mean ratios of the C_{max} and AUC parameters (data not shown), plasma concentrations of each formulation were averaged at each time point for all subjects.

Of the 24 subjects randomized in study 3, 12 were randomized to a formulation A → B sequence and 12 to a formulation B → A sequence. All 12 subjects in the sequence B → A group completed the study, but two of the 12 subjects in the sequence A → B group did not; one because of accidental

Table II. Pharmacokinetic parameters of armodafinil and modafinil determined from pooled, dose-normalized data for the three studies[a]

Pharmacokinetic parameter	Armodafinil 200 mg	Modafinil 200 mg	Geometric mean ratio[b] (90% CI)
C_{max} (μg/mL)[c]	5.44 ± 1.64	4.61 ± 0.73	1.14 (1.01, 1.28)
AUC_{last} (μg • h/mL)[c]	88.2 ± 29.6	66.5 ± 14.4	1.28 (1.11, 1.47)
AUC_{∞} (μg • h/mL)[c]	95.8 ± 28.0	68.5 ± 15.3	1.37 (1.22, 1.54)
t_{max} (h)[d]	1.8	2.5	
$t_{½\beta}$ (h)	13.0 ± 2.6	13.6 ± 2.0	

a Values are given as mean ± SD unless specified otherwise.

b Geometric mean ratio (armodafinil : modafinil) and its 90% CI are based on least squares mean difference (armodafinil – modafinil) of the log-transformed values using a linear model with treatment as factor.

c Determined from pooled plasma concentration data normalized to 200 mg doses of armodafinil or modafinil. For the bioequivalence investigations (studies 2 and 3), plasma drug concentrations for the two formulations used were averaged for each subject at each time point.

d Median values.

AUC_{last} = area under the plasma drug concentration vs time curve from time zero to time of the last measurable concentration; **AUC_{∞}** = area under the plasma drug concentration vs time curve from time zero to infinity; **CI** = confidence interval; **C_{max}** = maximum plasma drug concentration; **SD** = standard deviation; **$t_{½\beta}$** = terminal elimination half-life; **t_{max}** = time to reach C_{max}.

death as a result of a motor vehicle accident that occurred six days after drug administration, and one because of a protocol violation. Thus, all 24 subjects in study 3 received a 400 mg dose as formulation A, and 22 received the same dose as formulation B. Because the bioequivalence of the two formulations was demonstrated via 90% CIs in the range 0.8–1.25 for the geometric mean ratios of their AUC_{∞} and C_{max} values (data not shown), all 24 subjects were able to be evaluated for determination of pharmacokinetic parameters, and data for formulations A and B were averaged for each subject.

Pharmacokinetic Parameters of Armodafinil and Modafinil

From the pooled, dose-normalized data for studies 1 and 2, values for non-dose-dependent pharmacokinetic parameters (table II) of armodafinil were: t_{max} 1.8 hours (median); λ_z 0.0559 ± 0.0119 h^{-1}; and $t_{½\beta}$ 13.0 ± 2.6 hours. Corresponding values from study 3 for modafinil (averaged data for formulations A and B) were: t_{max} 2.5 hours (median); λ_z 0.053 ± 0.008 h^{-1}; and $t_{½\beta}$ 13.6 ± 2.0 hours.

Plasma concentration profiles of armodafinil and modafinil derived from pooled, dose-normalized data (i.e. plasma concentrations normalized to 200 mg doses of the two drugs) are shown in figure 1. The elimination profile of modafinil appeared to be biphasic, with an initial more rapid phase followed by a slower terminal phase (corresponding to elimination primarily of the *S*- and *R*-isomers, respectively). In contrast, the elimination of armodafinil appeared to be monophasic, resulting in higher plasma drug concentrations from about 4–6 hours after dosing onward. Dose-dependent pharmacokinetic parameters

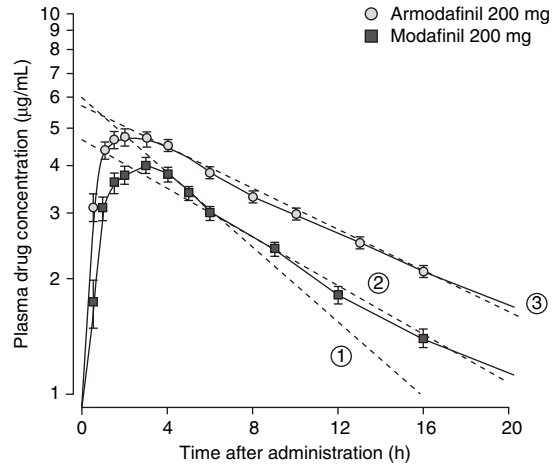

Fig. 1. Mean (± standard error of the mean) plasma concentrations following doses of armodafinil 200 mg and modafinil 200 mg (pooled, dose-normalized data from studies 1 and 2 of armodafinil and from study 3 of modafinil) over the first 20 hours after administration, suggesting a monophasic elimination profile following armodafinil administration and a biphasic elimination profile following modafinil administration. Dotted lines 1 and 2 represent the different elimination rates of the *S*- and *R*-isomers of modafinil, respectively; dotted line 3 represents the elimination rate of armodafinil.

of armodafinil and modafinil determined from the pooled, dose-normalized data (table II) indicate that, although there was little difference between the two drugs in C_{max}, there were marked differences in AUC_{last} and AUC_{∞}: values for armodafinil were 33% and 40% higher, respectively, compared with modafinil. The geometric mean ratios for both parameters were significantly higher following armodafinil than following modafinil administration (AUC_{last} 1.28, 90% CI 1.11, 1.47; AUC_{∞} 1.37, 90% CI 1.22, 1.54), indicating greater systemic exposure following armodafinil administration.

Adverse Events

The safety populations of the three studies were composed of all 30 subjects randomized to armodafinil in study 1; 28 and 29 subjects randomized in study 2 who received single doses of 5×50 mg tablets and 1×250 mg tablet of armodafinil, respectively; and 24 and 22 subjects randomized in study 3 who received single doses of modafinil 400 mg as formulation A and formulation B, respectively.

A summary of treatment-emergent adverse events reported at each dose level of armodafinil is shown in table III and for each formulation of modafinil in table IV. Both drugs were generally well tolerated, and the majority of adverse events were mild in intensity as determined by the investigators. The most common adverse event experienced with both drugs was headache, the occurrence of which appeared to be related to the dose of armodafinil in the ascending-dose study (study 1). Other, less common adverse events included dizziness, insomnia, nausea, anxiety and fatigue with armodafinil (table III), and dizziness, asthenia, nausea, nervousness, insomnia and confusion with modafinil (table IV). Serious adverse events reported in the three studies were a knee ligament injury and meniscus lesion in one subject in study 2, and a death resulting from accidental injury in study 3. None of the serious adverse events was considered by the respective investigator to be treatment related.

No clinically meaningful changes in serum chemistry, haematology or urinalysis tests, or in vital signs, ECG findings or physical examination findings, were detected with either drug. Although three abnormal laboratory test results were recorded with modafinil (a low haematocrit after formulation B in one subject, and an elevated creatine phosphokinase level in one subject each after formulation A or formulation B), none of these events was considered clinically significant. Gradual increases in heart rate with armodafinil were noted over the period 6–10 hours after administration in study 2, but thereafter heart rate values decreased to near-baseline at 16 hours. Decreased diastolic blood pressure in two subjects and decreased heart rate in one subject was observed in study 1 following armodafinil administration. A decrease in systolic blood pressure following modafinil administration (formulation A) was detected in one subject in study 3.

Discussion

Pharmacokinetic profiles generated from pooled, dose-normalized plasma drug concentration data in the three single-dose pharmacokinetic studies analysed suggest that modafinil exhibits a biphasic elimination profile, with an initial rapid decline from the peak (reflecting the faster clearance of the *S*-isomer) followed by a slower terminal phase decline due to the remaining longer-lasting *R*-isomer. In contrast, armodafinil appears to have a monophasic elimination profile, resulting in higher plasma drug concentrations compared with modafinil beginning approximately 4–6 hours after dosing. Greater systemic availability (as indicated by markedly higher AUC values) was observed following armodafinil compared with modafinil administration. In contrast, the C_{max} values of the two study drugs were similar, although the upper limit C_{max} CI value just missed the bioequivalence criteria range. It is notable that higher concentrations were measured later in the dosing period following armodafinil compared with modafinil administration despite the virtually identical $t_{½\beta}$ values of the two drugs: 13.0 hours versus 13.6 hours, respectively. These

Table III. Armodafinil studies: treatment-emergent adverse events [n (%)] occurring in ≥5% of subjects in any dose group (safety analysis sets)[a]

Adverse event	50 mg	100 mg[b]		200 mg	250 mg[c] fasted		300 mg	400 mg	Placebo
	fasted	fasted	fed	fasted	5×50 mg	1×250 mg	fasted	fasted	
	(n=6)	(n=6)	(n=6)	(n=6)	(n=28)	(n=29)	(n=6)	(n=6)	(n=10)
General/administration site									
Fatigue	0	0	0	0	4 (14)	6 (21)	0	0	0
Asthenia	0	0	0	0	0	0	0	1 (17)	0
Energy increased	0	0	0	0	3 (11)	2 (7)	0	0	0
Feeling jittery	0	0	0	0	0	3 (10)	0	0	0
Feeling hot	0	0	0	0	1 (4)	2 (7)	0	0	0
Chest discomfort	0	0	0	0	0	2 (7)	0	0	0
Thirst	0	0	0	0	1 (4)	1 (3)	0	1 (17)	0
Gastrointestinal									
Nausea	0	0	0	0	6 (21)	5 (17)	0	0	0
Abdominal pain, upper	0	0	0	0	4 (14)	2 (7)	0	0	0
Dry mouth	0	0	0	0	2 (7)	2 (7)	0	0	0
Dyspepsia	0	0	0	0	0	1 (3)	0	1 (17)	0
Investigations									
Heart rate increased	0	0	0	0	3 (11)	5 (17)	0	0	0
Musculoskeletal									
Back pain	1 (17)	0	0	0	1 (4)	1 (3)	0	0	0
Arthralgia	0	0	0	1 (17)	0	0	0	0	0
Myalgia	0	0	0	1 (17)	0	0	0	0	0
Pain in extremity	0	0	0	0	2 (7)	0	0	0	0
Nervous system									
Headache	1 (17)	1 (17)	0	2 (33)	11 (39)	11 (38)	3 (50)	2 (33)	0
Dizziness	0	0	0	0	7 (25)	8 (28)	1 (17)	1 (17)	0
Tremor	0	0	0	0	1 (4)	2 (7)	0	0	0
Hypaesthesia	0	0	0	1 (17)	0	0	0	0	0
Psychiatric									
Insomnia	0	0	0	0	6 (21)	6 (21)	0	0	0
Anxiety	0	0	0	1 (17)	5 (18)	0	0	0	0
Nervousness	0	0	0	0	0	2 (7)	0	0	0
Logorrhoea	0	0	0	0	2 (7)	0	0	0	0

Continued next page

Table III. Contd

Adverse event	50 mg fasted (n = 6)	100 mg[b] fasted (n = 6)	100 mg[b] fed (n = 6)	200 mg fasted (n = 6)	250 mg[c] fasted 5×50 mg (n = 28)	250 mg[c] fasted 1×250 mg (n = 29)	300 mg fasted (n = 6)	400 mg fasted (n = 6)	Placebo (n = 10)
Respiratory, thoracic									
Pharyngitis	0	0	0	0	0	0	1 (17)	0	0
Rhinitis	0	0	1 (17)	0	0	0	0	0	0
Skin/subcutaneous tissue									
Contact dermatitis	0	0	1 (17)	0	0	0	0	0	0
Pruritus	0	0	1 (17)	0	0	0	0	0	0

a Adverse events were classified according to Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) preferred terms for study 1, and Medical Dictionary for Regulatory Activities (MedDRA) terms for study 2. MedDRA and COSTART terms have been combined for the two armodafinil studies in this table (under MedDRA system organ class headings).

b Subjects in the 100 mg dose group of study 1 received the first dose of armodafinil after an overnight fast, and the second (1 week later) after consuming a standard fatty meal.

c Armodafinil bioequivalence crossover study (study 2): 5×50 mg coated tablets vs 1×250 mg uncoated tablet.

findings confirm and extend those of a previous *post hoc* pharmacokinetic analysis comparing plasma concentration profiles of armodafinil and modafinil after multiple-dose administration over 7 days, which showed that mean plasma concentrations of armodafinil at 7–11 hours after dosing were markedly higher than those of modafinil, and that plasma armodafinil concentrations exhibited less fluctuation and swing across a 24-hour dose interval than those of modafinil.[10]

With once-daily dosing in the morning, armodafinil may have advantages over modafinil in improving wakefulness throughout the day in patients with ES. Previous studies with modafinil have found that its wakefulness-promoting effect is not always sustained throughout the day, which may necessitate raising the dose and/or employing a less convenient dose-splitting regimen to alleviate ES effectively later in the day.[11,12] In contrast, studies of armodafinil in patients with ES associated with treated OSA or narcolepsy have demonstrated its effectiveness in improving wakefulness throughout the day, including both the early daytime period (9am–3pm) and the late-day period (3pm–7pm).[4,16]

The pooled safety data from the three randomized studies indicated that both armodafinil and modafinil were well tolerated after single doses, with the majority of adverse events reported being mild in intensity. The most frequent adverse event noted with both drugs was headache, which, in the case of armodafinil, appeared to be dose related. No serious adverse events attributed by the investigator to either drug were recorded.

Limitations of the present analysis include its *post hoc* nature, the across-study/across-subject design, and the fact that the dosage forms used in the two armodafinil studies were different, i.e. capsules in study 1 and tablets in study 2. However, the pharmacokinetic values determined in studies 1 and 2 were generally comparable, and any differences between the capsule and tablet formulations used were likely to be minimal; for example, the t_{max} and $t_{½\beta}$ values recorded in the two studies were very similar (t_{max} range 0.8–3.0 hours for the four doses administered in study 1 [excluding subjects given 100 mg

Table IV. Modafinil study: treatment-emergent adverse events [n (%)] occurring in ≥5% of subjects with either formulation (safety analysis set)[a]

Adverse event	400 mg[b] fasted	
	tablet A (n = 24)	tablet B (n = 22)
General/administration site		
Asthenia	2 (8)	2 (9)
Infection	2 (8)	0
Laboratory test abnormal	1 (4)	1 (5)
Blood and lymphatic system		
Anaemia	0	1 (5)
Eye disorders		
Eye haemorrhage	0	1 (5)
Gastrointestinal		
Nausea	1 (4)	2 (9)
Dyspepsia	0	1 (5)
Metabolism/nutrition		
Dehydration	0	1 (5)
Musculoskeletal		
Back pain	1 (4)	1 (5)
Nervous system		
Headache	5 (21)	5 (23)
Dizziness	2 (8)	2 (9)
Leg cramps	0	1 (5)
Paraesthesia	0	1 (5)
Psychiatric		
Nervousness	3 (13)	0
Confusion	0	3 (14)
Insomnia	2 (8)	1 (5)
Renal and urinary		
Urinary frequency	0	1 (5)
Respiratory, thoracic		
Rhinitis	0	1 (5)

a Adverse events were classified according to Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) preferred terms for this study (study 3), and COSTART terms have been included under the same Medical Dictionary for Regulatory Activities system organ class headings.

b Modafinil bioequivalence crossover study (study 3): formulation A = original tablet (2 × 200 mg) vs formulation B = test tablet (2 × 200 mg).

after a meal] vs 1.8–2.3 hours for the two 250 mg doses in study 2; $t_{½\beta}$ range 10.6–14.7 hours in study 1 vs 12.8–13.0 hours in study 2). Because the two bioequivalence studies (studies 2 and 3) recorded very similar plasma drug concentration versus time profiles for the two tablet formulations used and adequately demonstrated the bioequivalence of the formulations, any differences that may have existed between the formulations were also likely to be minimal. These potential differences were further minimized by averaging the plasma drug concentrations measured with each formulation in each subject at each time point.

It is important to note that the results of this analysis regarding tolerability cannot be assumed to reflect long-term use of either drug for the treatment of patients with ES. All subjects in this analysis were healthy volunteers who received only a single dose of

the study medications (or two single doses 7 days apart).

Conclusion

Armodafinil and modafinil have substantially different late-day pharmacokinetic profiles despite having similar early pharmacokinetic profiles and indistinguishable $t_{½\beta}$ values after single-dose administration in healthy adult subjects. Based upon a visual inspection of the respective profiles, modafinil appears to have a biphasic elimination profile, which is consistent with the rapid elimination of the *S*-isomer in the racemate, while armodafinil, the pure, longer-lasting *R*-isomer, appears to have a monophasic elimination profile and maintains higher plasma drug concentrations later in a dosing interval than modafinil on a milligram-to-milligram basis. The pharmacokinetic profile of armodafinil may result in improved wakefulness throughout the day in patients with ES compared with modafinil.

Acknowledgements

This analysis was sponsored by Cephalon, Inc., Frazer, PA, USA. All authors are employees of Cephalon, Inc. The authors wish to acknowledge Ryan Dammerman, MD, PhD (Cephalon, Inc. employee) for his contribution to the medical content of this paper and Thomson Reuters (Horsham, PA, USA) and Virginia Schobel (Cephalon, Inc. employee) for their editorial assistance. The authors would also like to acknowledge the work of the study investigators: Stephen Freestone, MD, Inveresk Research, Tranent, Scotland (study 1); Dennis Swearingen, MD, MDS Pharma Services, Phoenix, AZ, USA (study 2); and Krishna K. Talluri, MD, PPD Pharmaco, Inc., Morrisville, NC, USA (study 3).

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