CNS Drugs 2009; 23 (9): 793-803
1172-7047/09/0009-0793/$49.95/0

Armodafinil

Karly P. Garnock-Jones, Sohita Dhillon and *Lesley J. Scott*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Philadelphia, Pennsylvania, USA

Contents

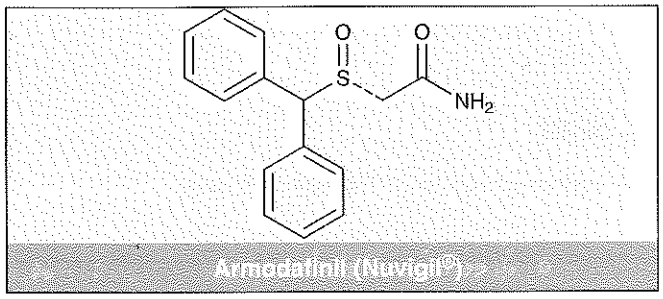
Abstract 793
1. Pharmacodynamic Profile 794
2. Pharmacokinetic Profile 795
3. Therapeutic Efficacy 797
4. Tolerability 801
5. Dosage and Administration 802
6. Armodafinil: Current Status 802

Abstract

- Armodafinil is the *R*-enantiomer of modafinil, a wake-promoting agent, that primarily affects areas of the brain involved in controlling wakefulness.
- Once-daily armodafinil was effective in improving wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome (OSA) [despite treatment of the underlying condition], narcolepsy or shift work sleep disorder (SWSD) in four large (n > 195), double-blind, multinational trials of 12 weeks' duration.
- Compared with placebo, mean sleep latency (coprimary endpoint) was significantly improved with armodafinil 150 or 250 mg once daily in patients with OSA or narcolepsy, and with armodafinil 150 mg once daily in patients with SWSD, as assessed by the Multiple Sleep Latency Test (MSLT) or the Maintenance of Wakefulness Test (MWT).
- Furthermore, a significantly higher proportion of armodafinil than placebo recipients achieved a response (at least a minimal improvement) on the Clinical Global Impressions of Change (CGI-C) scale at study end in these four trials (coprimary endpoint).
- Once-daily armodafinil was generally well tolerated in adult patients with excessive sleepiness associated with OSA (despite treatment of the underlying condition), narcolepsy or SWSD.

Features and properties of armodafinil (Nuvigil®)

Indications		
To improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome (despite treatment of the underlying condition), narcolepsy or shift work sleep disorder		
Mechanism of action		
Affects areas of the brain involved in controlling wakefulness		
Dosage and administration		
Dose	150 or 250 mg	
Frequency	Once daily	
Route	Oral	
Pharmacokinetic profile (single 150 or 250 mg dose in healthy volunteers)		
	150 mg	250 mg
Mean peak plasma concentration [μg/mL]	2.99	5.9
Median time to peak plasma concentration [h]	6.5	1.5
Mean area under the plasma concentration-time curve from time zero to 14 hours (150 mg) or infinity (250 mg) [μg • h/mL]	29.9	129.2
Adverse events (incidence ≥5% and higher than placebo)		
Headache, nausea, dizziness, insomnia		



Excessive sleepiness, while often due to insufficient night-time sleep, can be a symptom of many sleep disorders and other diseases, including obstructive sleep apnoea/hypopnoea syndrome (OSA), narcolepsy and shift work sleep disorder (SWSD).[1] The most common underlying cause of excessive sleepiness among patients referred to specialists is OSA.[1]

OSA is characterized by repetitive episodes of complete or partial upper airway obstruction during sleep, causing brief arousal from sleep.[2] Patients do not feel refreshed when they wake, and excessive sleepiness is very common. Narcolepsy is classified as a hypersomnia of central nervous origin, and is characterized by excessive daytime sleepiness with or without cataplexy.[2] Patients nap during the day and awake feeling refreshed, but are sleepy again within 2–3 hours. SWSD is classified as a circadian rhythm sleep disorder, with symptoms of insomnia or excessive sleepiness occurring transiently in relation to work schedules.[2] It is characterized by fatigue and functional impairment.

Initial treatment recommendations involve treatment of underlying causes (wherever possible), lifestyle interventions, and psychological and/or drug therapy (if required).[1] Historically, stimulants (sympathomimetics, amfetamines and amfetamine-like compounds) were used to treat excessive sleepiness associated with a sleeping disorder.[3] However, these have a potential for drug abuse, which was believed to be inseparable from the stimulant effects of the drugs.[3] Caffeine is known to sustain performance and alertness, though its role has been limited in some individuals because of unacceptable acute side effects including tremor, gastrointestinal symptoms and palpitations.[4]

The wake-promoting agent modafinil is an orally administered benzhydrylsulfinylacetamide.[5] It is a racemic compound containing equal amounts of *R*-modafinil and *S*-modafinil, with demonstrated efficacy in improving wakefulness and performance in patients with excessive sleepiness associated with OSA despite nasal continuous positive airway pressure therapy (nCPAP) and in patients with narcolepsy or SWSD[6] (partially reviewed by Keating and Raffin[5]). Recipients of modafinil experienced clinical improvement with no adverse effect on daytime sleep.[5]

Armodafinil (Nuvigil®) is the *R*-isomer of modafinil.[7] It has a half-life that is approximately three to four times longer than that of the *S*-isomer and may provide longer-lasting wake-promoting effects than those of modafinil when given once daily.[8,9]

This article provides an overview of the pharmacological properties of oral armodafinil and reviews the clinical trial data available on the efficacy and tolerability of the drug in patients with excessive sleepiness associated with OSA (despite treatment of the underlying condition), narcolepsy or SWSD. Medical literature on the use of armodafinil to improve wakefulness in these patients was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

Where data for the pharmacodynamic properties of armodafinil are limited, discussion focuses on the racemic compound modafinil, as reported in the manufacturer's prescribing information for armodafinil.[10]

- Although the exact mechanism by which armodafinil promotes wakefulness is unknown, it appears that the drug primarily affects areas of the brain involved in controlling wakefulness.[11] Armodafinil is classified as a non-narcotic schedule IV compound.[3]
- The pharmacodynamic profile of armodafinil differs from that of sympathomimetic amines (e.g. amfetamine and methylphenidate), although

armodafinil has wake-promoting actions similar to these agents.[10]

- At pharmacologically relevant concentrations, armodafinil does not bind to most of the potentially relevant receptors for sleep/wake regulation (e.g. serotonin, dopamine and adenosine receptors) or transporters of neurotransmitters or enzymes involved in sleep/wake regulation (e.g. serotonin, noradrenaline [norepinephrine] and phosphodiesterase VI transporters).[10]
- Armodafinil is not a direct- or indirect-acting dopamine receptor agonist; however, *in vitro*, it binds to the dopamine transporter, thereby inhibiting dopamine reuptake.[10] Modafinil requires dopamine transporters for its wake-promoting action and binds to the dopamine reuptake site, resulting in an increase in extracellular dopamine.[10]
- Modafinil does not appear to be a direct or indirect α_1-adrenergic agonist, although it has been suggested that the mechanism whereby it promotes wakefulness requires an intact α_1-adrenergic system;[5] modafinil action was attenuated by prazosin, an α_1-adrenergic antagonist.[10] Modafinil appears to enhance the inhibitory effect of noradrenaline on sleep-promoting neurons in the brain.[5]
- Small, but consistent increases in heart rate and systolic and diastolic blood pressure (SBP and DBP) were evident in placebo-controlled studies of armodafinil (see section 3 for study design details).[10] The average increase in heart rate compared with placebo was 0.9–3.5 beats per minute; the average increase in SBP and DBP was 1.2–4.3 mmHg.[10]
- The abuse potential of armodafinil has not been investigated; however, it is likely to be similar to that of modafinil.[10] The potential for abuse and dependency appears to be lower for modafinil than amfetamine-like stimulants.[12]
- Armodafinil significantly increases the expression of Fos, a marker of neuronal activation.[11] The number of Fos-labelled neurons increased in brain arousal centres in rats administered a wake-promoting dose of armodafinil compared with those administered vehicle.
- In a rat model, intraperitoneal armodafinil dose dependently increased wakefulness when compared with vehicle (abstract presentation).[13] Moreover, there was no induction of hyperthermia or increased locomotor activity at a dose that produced a degree of wake-enhancement similar to that produced by the stimulant *d*-metamfetamine; nor was armodafinil-induced wakefulness followed by acute rebound hypersomnolence, all of which were observed during *d*-metamfetamine administration.[13]
- In 107 healthy volunteers, relative to placebo, a single dose (100–300 mg) of armodafinil significantly ($p < 0.0001$) improved wakefulness in a randomized, double-blind study ($n = 17–18$ /group).[7] In addition, while both armodafinil 200 mg and modafinil 200 mg were associated with a decrease (after the initial increase) in sleep latency across the night, the change in latency was significantly ($p = 0.02$) smaller with armodafinil than with modafinil.[7] For discussion of the effects of armodafinil in patients with OSA (despite treatment of the underlying condition), narcolepsy and SWSD see section 3.

2. Pharmacokinetic Profile

The pharmacokinetics of armodafinil have only been investigated in healthy volunteers.[7,9,14] Where data for armodafinil are not available, data for modafinil (from the armodafinil prescribing information[10]) are reported, as these data should be applicable to armodafinil as well. The pharmacokinetics of the modafinil isomer *R*-modafinil (when modafinil was administered) are also reported and compared with those of the other isomer *S*-modafinil.[9] Discussion focuses on recommended dosages (section 5).

- Oral armodafinil is rapidly absorbed and exhibits linear pharmacokinetics after single and multiple 50–400 mg doses.[14] As armodafinil is insoluble, intravenous administration was not possible, thus preventing determination of absolute oral bioavailability.[10] Over 12 weeks of treatment, no time-dependent pharmacokinetic changes were observed,[10] and steady state was reached within 7 days.[14] The

steady-state systemic exposure is 1.8-fold higher than that after a single dose.[14]

- After a single dose of armodafinil 150 mg, values for the mean maximum plasma concentration (C_{max}), mean area under the plasma concentration-time curve from time zero to 14 hours (AUC_{14}) and median time to attain C_{max} (t_{max}) were 2.99 μg/mL, 29.9 μg • h/mL and 6.5 (range 3–11) hours, respectively.[7] Multiple-dose data are not available for this dosage.
- Single (day 1) and multiple (day 7) doses of armodafinil 250 mg/day resulted in a mean C_{max} of 5.9 and 9.2 μg/mL and a mean AUC from time zero to infinity (AUC_{∞}; single dose) and over time period τ (AUC_{τ}; multiple doses) of 129.2 and 148.3 μg • h/mL.[14] The median t_{max} values were 1.5 (range 0.5–6.0) and 2 (range 0.5–6.0) hours, respectively.
- In a study investigating a once-daily dose of modafinil (200–800 mg) for 7 days, *R*-modafinil was rapidly absorbed and widely distributed in body tissues.[9] Steady-state plasma levels were attained after the third dose for *R*-modafinil, compared with the first dose for *S*-modafinil, and the elimination of *R*-modafinil was approximately three times slower than that of the *S*-enantiomer (terminal elimination half-life of 13–16 vs 4.0–4.2 hours after a single dose [day 1] and 15–16 vs 4.3–4.9 hours after multiple doses [day 7]).[9]
- When administered with food, the overall bioavailability of armodafinil is not affected; however, as the t_{max} is delayed by ≈2–4 hours,[14] it is possible that food may affect the onset and time course of armodafinil pharmacological action.[10]
- The apparent volume of distribution after a single dose of armodafinil (normalized to 50 mg) is ≈42 L.[14] While armodafinil protein-binding data are not available, approximately 60% of modafinil is bound to plasma protein *in vitro*, predominantly to albumin.[10]
- Armodafinil metabolism data are not available. However, modafinil is metabolized primarily by the liver; <10% of the parent compound is excreted in the urine.[10] By 11 days post-dose, 80% of a radiolabelled dose of modafinil was excreted in the urine and 1% in the faeces.
- Armodafinil undergoes hydrolytic deamidation, *S*-oxidation and aromatic ring hydroxylation followed by glucuronide conjugation of the hydroxylated products.[10] The most prominent pathway is amide hydrolysis; the second most prominent is sulfone formation by the cytochrome P450 (CYP) isoenzymes CYP3A4 and CYP3A5. Two metabolites of armodafinil reach appreciable concentrations in plasma: *R*-modafinil acid and modafinil sulfone.[10]
- The apparent terminal elimination half-life of armodafinil is ≈15 hours, and the oral clearance at steady state is ≈33 mL/min.[10,14]

Special Patient Populations

- There are no sex-based differences in the pharmacokinetic profile of armodafinil.[10]
- Pharmacokinetic data for armodafinil in other special patient populations are not available; therefore, relevant data for modafinil are discussed.[10]
- It was considered unlikely that the changes in the oral clearance or C_{max} values of modafinil in elderly patients (67–87 years) versus historically matched younger adults would be of clinical significance, as they may have been due to potential effects from the multiple concomitant medications taken.[10] However, oral clearance may be reduced in this population.
- Exposure to the inactive metabolite modafinil acid, but not modafinil, was increased after a single modafinil 200 mg dose in patients with severe chronic renal failure (creatinine clearance ≤20 mL/min [≤1.2 L/h]), though the clinical relevance of this is unknown.[10]
- Dosage reductions are recommended in patients with severe hepatic impairment with or without cirrhosis, since clearance of modafinil has been shown to be reduced relative to that of healthy participants.[10]

Drug Interactions

- As there are multiple pathways by which armodafinil is metabolized and as a non-CYP-related pathway is the most rapid metabolic pathway, the likelihood of concomitant medications substantially altering the overall pharmacokinetics of armodafinil via CYP inhibition is low.[10]
- Armodafinil 250 mg/day did not induce CYP1A2, moderately induced CYP3A4 and moderately inhibited CYP2C19.[15] Thus, the pharmacokinetics of drugs that are substrates of CYP3A4/5 (e.g. steroidal contraceptives, midazolam, ciclosporin and triazolam) or CYP2C19 (e.g. omeprazole, diazepam and phenytoin) may be affected when co-administered with armodafinil. These drugs may therefore require dosage adjustments (section 5).
- There is also a potential for drug interactions between armodafinil and drugs that are inhibited, induced or metabolized by CYP2B6 and CYP2C9. Data are lacking for armodafinil; however, modafinil modestly induces CYP2B6 and suppresses CYP2C9 in *in vitro* studies.[16]
- The potential for armodafinil interactions with highly protein-bound drugs is considered minimal.[10] Caution should be used when co-administering armodafinil and monoamine oxidase inhibitors, as data specific to drug-drug interaction potential are not available.[10]
- Armodafinil most likely has no clinically relevant effects on the pharmacokinetic profile of CNS active drugs, such as methylphenidate and dexamfetamine. When these drugs were coadministered with modafinil in a pharmacokinetic model, no clinically relevant effects on the concomitant drugs were observed; however, modafinil absorption was delayed for ≈1 hour.[10]
- Concomitant modafinil had no effect on the pharmacokinetic profile of *R*- or *S*-warfarin, though it is recommended that prothrombin times or the international normalized ratio are monitored more frequently when armodafinil and warfarin are coadministered.[10]

3. Therapeutic Efficacy

The efficacy of armodafinil has been investigated in four 12-week, randomized, double-blind, placebo-controlled, multinational studies. Eligible patients (aged 18–65 years) were diagnosed with OSA,[20,21] narcolepsy[19] or SWSD[18] according to International Classification of Sleep Disorders criteria and had a Clinical Global Impressions of

Table I. Definition and description of efficacy rating scale and other relevant abbreviations used in clinical studies

Term	Definition	Description
CGI-C	Clinical Global Impressions of Change scale	Seven-point scale for rating the change in severity of illness, taking into account the total clinical experience. Rating is from 1 (very much improved) to 7 (very much worsened)
CGI-S	Clinical Global Impressions of Severity scale	Seven-point scale for rating the severity of illness, taking into account the total clinical experience. Rating is from 1 (normal) to 7 (extremely ill)
ESS	Epworth Sleepiness Scale	Eight-item rating scale measuring the likelihood of falling asleep in certain situations. Each item is rated from 0 (would never doze) to 3 (high chance of dozing); final score 0–24
KSS	Karolinska Sleepiness Scale	Nine-point scale for rating the level of sleepiness in the 5 minutes before the test. Rating is from 1 (very alert) to 9 (very sleepy, great effort to stay awake, fighting sleep)
MSLT	Multiple Sleep Latency Test	An objective assessment of sleepiness. The patient is instructed to lie quietly and attempt to sleep in five 20-minute naps at 2-hour intervals. Sleep latency is the time taken to reach either three consecutive 30-second epochs of stage 1 sleep or any single 30-second epoch of stage 2, 3, 4 or REM sleep[17,18]
MWT	Maintenance of Wakefulness Test	An objective measure of sleepiness. The patient is instructed to try to remain awake in a darkened room while in a semireclined position in six 20-[19] or 30-[20,21] minute periods at 2-hour intervals. Sleep latency is the time taken to reach either three consecutive epochs of stage 1 sleep or any epoch of stage 2, 3, 4 or REM sleep

REM = rapid eye movement.

Severity (CGI-S) scale score ≥4 (representing moderately ill or worse).[18-21] Patients received armodafinil 150[18-21] or 250[19,21] mg once daily or matching placebo.[18-21] Dosage was initiated at 50 mg/day and increased to 100 mg/day on day 2, followed by 50 mg/day increments every second day until the target dosage was achieved.[18-21] Treatment was administered in the morning in the studies in patients with OSA[20,21] or narcolepsy[19] and before the start of the night shift in the study in patients with SWSD.[18]

Key efficacy measures (including acronyms and definitions) used in the trials are listed in table I. The primary endpoints were the change from baseline to final visit in MWT (using the first 4 of 6 subtests)[19-21] or MSLT (using the last 4 of 5 subtests)[18]-assessed mean sleep latency, and the CGI-C scale response rate (response was defined as at least a minimal improvement on the CGI-C at the final visit).[18-21] Other endpoints included ESS[19-21] and KSS[18] scores and the change from baseline to final visit in MWT-assessed mean late-day sleep latency (using the last three of the six subtests).[19-21]

Efficacy assessments were based on the modified intent-to-treat (mITT) population using last-observation-carried-forward (LOCF) imputation.[18-21] Where stated, patient characteristics were generally comparable between treatment groups in each study.[19-21] The study in patients with narcolepsy reported a significant difference in age between groups at baseline; however, this was shown to have no effect on MWT results.[19]

In Patients with Obstructive Sleep Apnoea/Hypopnoea Syndrome

Patients diagnosed with OSA were required to have an ESS score ≥10, despite effective (Apnoea-Hypopnoea Index score ≤10 on night-time polysomnography) and regular (≥4 h/night on 70% of nights in a 2-week period) use of nCPAP treatment for ≥4 weeks.[20,21] Exclusion criteria included: medical or psychiatric disorders other than OSA that could cause excessive sleepiness;[20,21] other clinically significant, uncontrolled medical or psychiatric disorders;[20,21] caffeine consumption exceeding 600 mg/day;[20,21] or current use of drugs disallowed by the protocol.[20]

At baseline, 49–60% of patients in the armodafinil and placebo groups had a CGI-S rating of 'moderately ill', 26–33% were 'markedly ill', 10–17% were 'severely ill' and 2% were 'among the most extremely ill'.[20,21] Baseline ESS sleepiness scores in these patients were 15.3–16.0 and mean MWT-assessed sleep latencies were 21.5–23.7 min.[20,21]

- Armodafinil was associated with improved ($p < 0.001$) wakefulness in terms of mean MWT-assessed sleep latency compared with placebo in patients with OSA who were receiving adjunctive nCPAP therapy (coprimary endpoint) [figure 1a].[20,21] A significant ($p < 0.05$) difference from placebo was evident from week 4 onward in armodafinil 250 mg/day recipients,[21] and, for the most part, in armodafinil 150 mg/day recipients (except at the week 8 timepoint in one study[21]).[20,21] No significant difference between armodafinil 150 mg/day and armodafinil 250 mg/day recipients in mean MWT-assessed sleep latency was observed.[21]
- The proportion of patients classified as at least minimally improved on the CGI-C was significantly ($p < 0.01$) greater in armodafinil 150 and 250 mg/day than placebo recipients (coprimary endpoint) [figure 1b].[20,21]
- With regard to late-day MWT-assessed sleep latency, no significant differences between armodafinil 150 or 250 mg/day and placebo were found at the final visit in the individual studies (figure 2).[20,21] However, a pooled analysis of the two studies revealed that armodafinil 150 mg/day significantly ($p < 0.05$) improved wakefulness relative to placebo with regard to late-day MWT-assessed latency (+1.2 vs −0.3 minutes; extrapolated from graph).[22]
- Both armodafinil 150 and 250 mg/day recipients demonstrated significant ($p < 0.01$) improvements in patient-estimated sleepiness versus those receiving placebo.[20,21] The changes in ESS scores from baseline to final visit were −5.3[20]

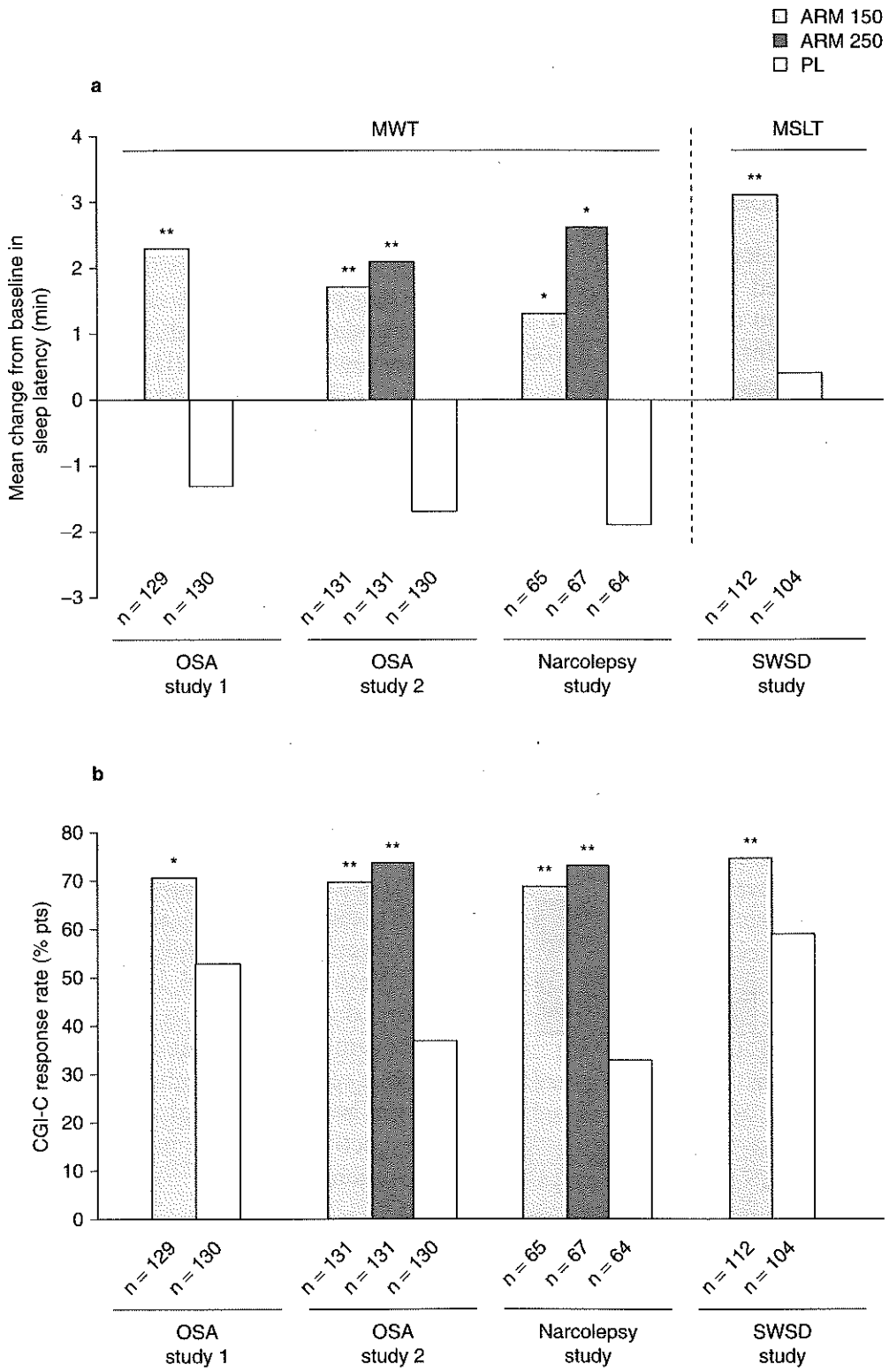


Fig. 1. Primary efficacy of armodafinil (ARM) vs placebo (PL). Twelve-week, randomized, double-blind, multinational studies in patients (pts) with excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome (OSA; OSA study 1[20] and OSA study 2[21]) [despite treatment of the underlying condition], narcolepsy[19] or shift work sleep disorder (SWSD).[18] (**a**) Mean change from baseline to last visit in sleep latency (coprimary endpoint), measured using the first 4 of 6 Maintenance of Wakefulness Test (MWT) subtests (baseline values in OSA pts of 21.5–23.7 min[20,21] and in narcolepsy pts of 9.5–12.5 min[19]) or the last 4 of 5 Multiple Sleep Latency Test (MSLT) subtests (baseline values 2.3 [ARM 150] and 2.4 [PL] min).[18] (**b**) Clinical Global Impressions of Change (CGI-C) scale response rate (coprimary endpoint); response was defined as at least a minimal improvement on the CGI-C at the final visit. Pts were randomized to once-daily treatment with ARM 150 (ARM 150)[18-21] or 250 (ARM 250)[19,21] mg/day or matching PL.[18-21] * $p < 0.01$, ** $p \leq 0.001$ vs PL.

and −5.5[21] in armodafinil 150 mg/day recipients, −5.5 in armodafinil 250 mg/day recipients[21] and −3.0[20] and −3.3[21] in placebo recipients (extrapolated from graphs).

In Patients with Narcolepsy

Patients with narcolepsy were required to have an MSLT-assessed mean sleep latency of ≤6 minutes.[19] Exclusion criteria included: medical or psychiatric disorders other than narcolepsy that could cause excessive sleepiness; other clinically significant, uncontrolled medical or psychiatric disorders; caffeine consumption exceeding 600 mg/day; or current use of drugs disallowed by the protocol.[19] Patients who reported cataplexy while on stable doses of anticataplectic medication (excluding sodium oxybate) were not excluded; however, anticataplectic medication was only permitted if it did not contribute to patient sleepiness and if the dosage was stable for ≥1 month.[19]

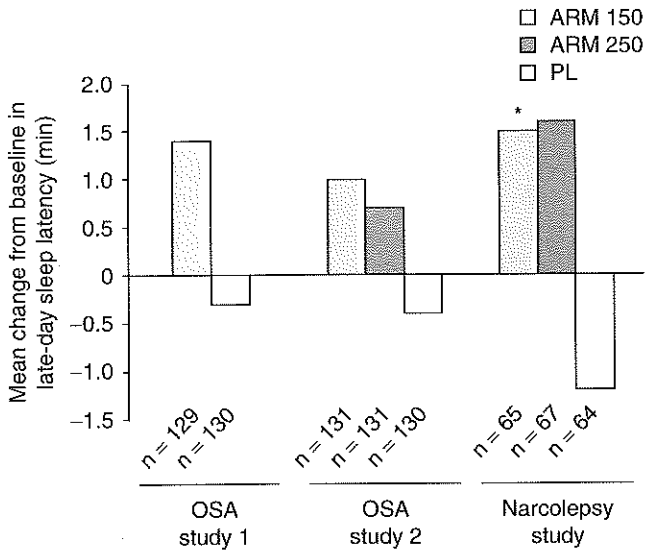


Fig. 2. Efficacy of armodafinil (ARM) vs placebo (PL). Twelve-week, randomized, double-blind, multinational studies in patients (pts) with excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome (OSA; OSA study 1[20] and OSA study 2[21]) [despite treatment of the underlying condition] or narcolepsy.[19] Mean change from baseline to last visit in late-day sleep latency, measured using the final three of six Maintenance of Wakefulness Test (MWT) subtests (baseline values in OSA pts of 23.4–25.4 min[20,21] and in narcolepsy pts of 10.5–12.9 min[19]). Pts were randomized to once-daily treatment with ARM 150 (ARM 150)[19-21] or 250 (ARM 250)[19,21] mg/day or matching PL.[19-21] * $p < 0.05$ vs PL.

At baseline, 29–37% of patients in the armodafinil and placebo groups had a CGI-S rating of 'moderately ill', 43–54% were 'markedly ill', 17–18% were 'severely ill' and 0–3% were 'among the most extremely ill'.[19] Baseline ESS sleepiness scores in these patients were 15.7–17.5 and mean MWT-assessed sleep latencies were 9.5–12.5 min.[19]

- In patients with narcolepsy, recipients of armodafinil 150 and 250 mg/day experienced a significantly ($p < 0.01$) greater improvement in mean MWT-assessed sleep latency and had higher ($p < 0.001$) CGI-C response rates than placebo recipients (coprimary endpoints) [figure 1].[19]
- Furthermore, the significant ($p < 0.05$) improvement from baseline in mean sleep latency compared with placebo recipients was observed from the first visit at week 4 till study end in armodafinil 150 mg/day recipients; armodafinil 250 mg/day recipients only significantly ($p < 0.05$) differed from placebo at week 4 and at the final visit.[19]
- Mean late-day MWT-assessed latency was also significantly ($p < 0.05$) improved among armodafinil 150 mg/day versus placebo recipients at the final visit; armodafinil 250 mg/day recipients did not differ significantly from placebo recipients for this endpoint (figure 2).[19]
- Both armodafinil 150 and 250 mg/day recipients demonstrated a significant ($p < 0.01$) improvement in patient-estimated sleepiness versus those receiving placebo[19] (change in ESS scores from baseline to final visit of −4.1[19] and −3.8,[19] respectively; change in ESS score among placebo recipients was −1.9[23]).

In Patients with Shift Work Sleep Disorder

Patients with SWSD were required to have an MSLT-assessed mean sleep latency of ≤6 minutes and a sleep efficiency of ≤87.5% on daytime polysomnography, to have complained of excessive sleepiness during night shifts for ≥3 months and were working for ≥5 nights per month (shift duration ≥6 and ≤12 hours); night shifts had to be consecutive for ≥3 nights.[18] Exclusion criteria included: clinically significant, uncontrolled medical

or psychiatric disorders; current sleep disorder other than SWSD; caffeine consumption exceeding 600 mg/day; or current use of drugs disallowed by the protocol.[18]

At baseline, 56% of armodafinil and 57% of placebo recipients had a CGI-S rating of 'moderately ill', 34% and 36% were 'markedly ill', 9% and 7% were 'severely ill', and <1% were 'among the most extremely ill'.[18] Baseline KSS sleepiness scores were 7.4 (in armodafinil recipients) and 7.3 (in placebo recipients) and mean MSLT-assessed sleep latencies were 2.3 and 2.4 minutes.[18]

- At final visit, armodafinil recipients showed significant ($p < 0.001$) improvement in wakefulness in terms of mean MSLT-assessed sleep latency compared with placebo recipients in patients with SWSD (coprimary endpoint) [figure 1a].[18] Moreover, a significant ($p < 0.05$) improvement from baseline in mean sleep latency in armodafinil compared with placebo recipients was observed from the first visit at week 4 till study end and throughout the night at final visit.[18]
- A greater ($p = 0.001$) proportion of armodafinil than placebo recipients showed an overall improvement in clinical condition as assessed by the CGI-C (coprimary endpoint) [figure 1b].[18]
- Patients receiving armodafinil also showed significant improvement in patient-estimated sleepiness compared with those receiving placebo.[18] The mean change from baseline in KSS score at study end was −1.8 for armodafinil recipients versus −1.0 for placebo recipients ($p < 0.01$); a significant improvement in sleepiness was apparent from week 4 till study end ($p < 0.01$).[18]

4. Tolerability

Armodafinil was generally well tolerated in clinical trials discussed in section 3, with the focus in this section being on a descriptive analysis of data pooled from all four placebo-controlled trials, as presented in the prescribing information.[10]

- Common (≥5% of armodafinil recipients) treatment-emergent adverse events that occurred more frequently in the armodafinil than placebo group during 12 weeks' treatment are summarized in figure 3.[10] Treatment-emergent adverse events were generally mild to moderate in severity. No serious adverse events considered treatment related were reported in the clinical trials.[18-21]

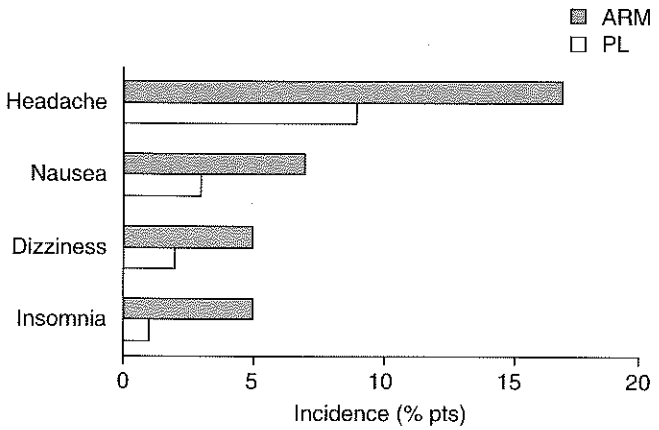


Fig. 3. Tolerability profile of armodafinil (ARM). Treatment-emergent adverse events that occurred in ≥5% of ARM 150 or 250 mg once-daily recipients (n = 645) and more frequently in ARM than in placebo (PL) recipients (n = 445) in a pooled analysis[10] of four 12-week, randomized, double-blind trials in patients (pts) with obstructive sleep apnoea (despite treatment of the underlying condition),[20,21] narcolepsy[19] or shift work sleep disorder.[18] Descriptive analysis only.

- Discontinuation of treatment as a result of adverse events occurred in 7% of armodafinil and 4% of placebo recipients; the most common adverse event leading to discontinuation was headache.[10] Adverse events that were potentially dose dependent were headache, rash, depression, dry mouth, insomnia and nausea.[10]
- Most laboratory parameters were generally similar in armodafinil and placebo groups.[10] Mean plasma gamma glutamyltransferase and alkaline phosphatase levels were higher than baseline in armodafinil recipients, although no change from baseline was observed in placebo recipients.[10] No ECG abnormalities were evident during armodafinil treatment.[10]
- While no serious skin rashes have been reported in clinical trials of armodafinil, those investigating modafinil have reported serious rash (including one paediatric case of possible Stevens-Johnson Syndrome) requiring hospitalization and discontinuation of treatment.[10] Armodafinil has been associated with benign rashes. As it is difficult to determine the severity of rashes, armodafinil should be discontinued at first sign of rash.
- As armodafinil is closely related to modafinil, multi-organ hypersensitivity reactions and

psychiatric symptoms cannot be ruled out.[10] Also, among all patients exposed to armodafinil, there has been one report each of angioedema and hypersensitivity (with rash, dysphagia and bronchospasm). Therapy should be discontinued in these instances.

5. Dosage and Administration

In patients with excessive sleepiness associated with OSA or narcolepsy, the recommended dosage of armodafinil in the US is 150 or 250 mg/day, given as a single dose in the morning.[10] Patients with OSA are expected to be receiving adjunctive therapy with standard treatment for the underlying disorder, for example, nCPAP. In patients with SWSD, the recommended dosage is 150 mg/day, administered ≈1 hour before the start of the work shift. Long-term use of armodafinil has not been investigated with regard to efficacy; therefore, periodical re-evaluations may be required when used for extended durations, to assess long-term benefit to the patient.[10]

Dosage adjustment may be required in patients receiving concomitant medications that are substrates for CYP3A4 or CYP3A5 (e.g. steroidal contraceptives, triazolam or ciclosporin) or drugs that are largely eliminated via CYP2C19 metabolism (e.g. diazepam, propranolol or phenytoin).[10,15] Patients with severe hepatic disease should receive a reduced dosage, as, potentially, should elderly patients.[10]

As patients may have more than one sleep disorder that is contributing to the excessive sleepiness, prescribers must pay careful attention to diagnosis and treatment.[10]

Armodafinil has not been studied in paediatric patients, nor is it approved in this patient group for any indication.[10]

Local prescribing information should be consulted for detailed information, including further contraindications, precautions, drug interactions and use in special patient populations.

6. Armodafinil: Current Status

Armodafinil is approved in the US to improve wakefulness in adult patients with excessive sleepiness associated with OSA (in conjunction with standard treatment[s] for underlying obstruction), narcolepsy or SWSD.[10] Armodafinil was more effective than placebo at improving sleep latency, was associated with higher CGI-C response rates and was generally well tolerated in four well designed studies in patients with excessive sleepiness associated with OSA (despite nCPAP therapy), narcolepsy or SWSD.

Acknowledgements and Disclosures

The manuscript was reviewed by: ***M.D. Lemon***, College of Pharmacy, South Dakota State University, Veterans Affairs Black Hills Health Care System, Fort Meade, South Dakota, USA; ***K.P. Strohl***, Department of Medicine, Case Western Reserve University, Cleveland, Ohio, USA.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article. Any changes resulting from comments received were made on the basis of scientific and editorial merit.

References

1. Managing excessive daytime sleepiness in adults. Drug Ther Bull 2004 Jul; 42 (7): 52-6
2. American Academy of Sleep Medicine. International classification of sleep disorders. 2nd ed. Diagnostic and coding manual. Westchester (IL): American Academy of Sleep Medicine, 2005
3. Nishino S, Okuro M. Armodafinil for excessive daytime sleepiness. Drugs Today 2008 Jun; 44 (6): 395-414
4. Sherman BW, Strohl KP. Management of shift work sleep disorder: Alice in Wonderland redux? J Occup Environ Med 2004 Oct; 46 (10): 1010-2
5. Keating GM, Raffin MJ. Modafinil: a review of its use in excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome and shift work sleep disorder. CNS Drugs 2005; 19 (9): 785-803
6. Cephalon Inc. Provigil® (modafinil tablets): US prescribing information [online]. Available from URL: http://provigil.com/media/PDFs/prescribing_info.pdf [Accessed 2009 Jun 22]
7. Dinges DF, Arora S, Darwish M, et al. Pharmacodynamic effects on alertness of single doses of armodafinil in healthy subjects during a nocturnal period of acute sleep loss. Curr Med Res Opin 2006 Jan; 22 (1): 159-67
8. Wong YN, King SP, Simcoe D, et al. Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. J Clin Pharmacol 1999 Mar; 39 (3): 281-8
9. Wong YN, Simcoe D, Hartman LN, et al. A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. J Clin Pharmacol 1999 Jan; 39 (1): 30-40

10. Cephalon Inc. Nuvigil® (armodafinil tablets): US prescribing information [online]. Available from URL: http://nuvigil.com/pdf/PI.pdf [Accessed 2009 Apr 9]
11. Fiocchi EM, Lin YG, Aimone L, et al. Armodafinil promotes wakefulness and activates Fos in rat brain. Pharmacol Biochem Behav 2009 Feb 26; 92 (3): S49-57
12. Myrick H, Malcolm R, Taylor B, et al. Modafinil: preclinical, clinical, and post-marketing surveillance: a review of abuse liability issues. Ann Clin Psychiatry 2004 Apr-Jun; 16 (2): 101-9
13. Wisor JP, Dement WC, Aimone L, et al. R-modafinil (armodafinil) produces dose-dependent increases in wake in rat without rebound hypersomnolence [abstract no. 310.3]. 2005 Annual Meeting of the Society for Neuroscience; 2005 Nov 12-16; Washington, DC
14. Darwish M, Kirby M, Hellriegel ET, et al. Pharmacokinetic profile of armodafinil in healthy subjects: pooled analysis of data from three randomized studies. Clin Drug Investig 2009; 29 (2): 87-100
15. Darwish M, Kriby M, Robertson Jr P, et al. Interaction profile of armodafinil with medications metabolized by cytochrome P450 enzymes 1A2, 3A4 and 2C19 in healthy subjects. Clin Pharmacokinet 2008; 47 (1): 61-74
16. Robertson Jr P, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet 2003; 42 (2): 123-37
17. US FDA. US FDA clinical review of armodafinil [online]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021875s000_MedR_P2.pdf [Accessed 2009 Jun 24]
18. Roth T, Czeisler CA, Walsh JK, et al. Randomized, double-blind, placebo-controlled study of armodafinil for the treatment of excessive sleepiness associated with chronic shift work sleep disorder [abstract no. 161]. Neuropsychopharmacology 2005; 30 Suppl. 1: S140. Plus poster presented at the 44th Annual Meeting of the American College of Neuropsychopharmacology; 2005 Dec 11-15; Waikoloa (HI)
19. Harsh JR, Hayduk R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. Curr Med Res Opin 2006 Apr; 22 (4): 761-74
20. Hirshkowitz M, Black JE, Wesnes K, et al. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. Respir Med 2007 Mar; 101 (3): 616-27
21. Roth T, White D, Schmidt-Nowara W, et al. Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. Clin Ther 2006 May; 28 (5): 689-706
22. Bogan R, Hirshkowitz M, Neibler G, et al. Armodafinil improves wakefulness and memory in nCPAP compliant patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome [abstract no. 805]. Proceedings of the American Thoracic Society 2006 Apr 1; 3 (Abstr. Suppl.): 872. Plus poster presented at the International Conference of the American Thoracic Society; 2006 May 19-24; San Diego (CA)
23. Data on file, Cephalon Inc., 2009

Correspondence: *Karly P. Garnock-Jones*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz