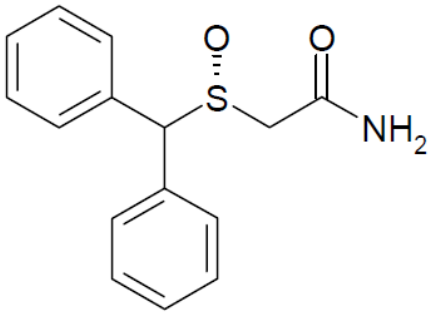
NUVIGIL®
armodafinil

PRODUCT INFORMATION

NAME OF THE MEDICINE

NUVIGIL® (armodafinil) is a wakefulness-promoting agent for oral administration. Armodafinil is the (*R*)-enantiomer of modafinil (MODAVIGIL®) which is a 1:1 mixture of the (*R*)- and (*S*)-enantiomers. The chemical name for armodafinil is 2-[(*R*)-(diphenylmethyl)sulfinyl]acetamide. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.35. The chemical structure is:



The CAS registry number is 112111-43-0.

DESCRIPTION

Armodafinil exists in multiple crystalline forms. Form 1, which is used in NUVIGIL®, is the least soluble form of armodafinil and is a white to off-white, crystalline powder that is slightly soluble in water, sparingly soluble in acetone and soluble in methanol. At least 90% of the armodafinil particles used in NUVIGIL® have a diameter of less than 200 microns.

NUVIGIL® tablets contain 50, 150 or 250 mg of armodafinil and the following inactive ingredients: croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, povidone, and pregelatinised maize starch.

PHARMACOLOGY

Pharmacodynamics

The mechanism(s) through which armodafinil promotes wakefulness is unknown. Armodafinil [(*R*)-modafinil)] has pharmacological properties similar to those of modafinil [a mixture of (*R*)- and (*S*)-modafinil] to the extent tested in animal and *in vitro* studies. The (*R*)- and (*S*)-enantiomers have similar pharmacological actions in animals.

Armodafinil and modafinil have wake-promoting actions similar to sympathomimetic agents including amphetamine and methylphenidate, although their pharmacologic profile is not identical to that of the sympathomimetic amines.

Modafinil-induced wakefulness can be attenuated by the α1-adrenergic receptor antagonist, prazosin; however, modafinil is inactive in other *in vitro* assay systems known to be responsive to α-adrenergic agonists such as the rat vas deferens preparation.

Armodafinil is an indirect dopamine receptor agonist; both armodafinil and modafinil bind *in vitro* to the dopamine transporter and inhibit dopamine reuptake. For modafinil, this activity has been associated *in vivo* with increased extracellular dopamine levels in some brain regions of animals. In genetically

engineered mice lacking the dopamine transporter (DAT), modafinil lacked wake-promoting activity, suggesting that this activity was DAT-dependent. However, the wake-promoting effects of modafinil, unlike those of amphetamine, were not antagonized by the dopamine receptor antagonist haloperidol in rats. In addition, alpha-methyl-p-tyrosine, a dopamine synthesis inhibitor, blocks the action of amphetamine, but does not block locomotor activity induced by modafinil.

In addition to its wake-promoting effects and ability to increase locomotor activity in animals, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants in humans. Modafinil has reinforcing properties, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; modafinil was also partially discriminated as stimulant-like (see Abuse and Dependence Potential).

Based on nonclinical studies, two major metabolites, acid and sulfone, of modafinil or armodafinil, do not appear to contribute to the CNS-activating properties of the parent compounds.

Pharmacokinetics

Armodafinil exhibits linear time-independent kinetics following single and multiple oral dose administration. Increase in systemic exposure is proportional over the dose range of 50 to 400 mg. No time-dependent change in kinetics was observed through 12 weeks of dosing. Apparent steady state for armodafinil was reached within 7 days of dosing. At steady state, the systemic exposure for armodafinil is 1.8 times the exposure observed after a single dose. The concentration-time profiles of the (*R*)-enantiomer following administration of a single-dose of 50 mg NUVIGIL® or 100 mg MODAVIGIL® [modafinil, a 1:1 mixture of (*R*)- and (*S*)-enantiomers] are nearly superimposable. However, the C_{max} and $AUC_{0-\infty}$, of armodafinil at steady-state were approximately 37% and 70% higher, respectively, following administration of 200 mg NUVIGIL® than the corresponding values of modafinil following administration of 200 mg modafinil due to the more rapid clearance of the (*S*)-enantiomer (elimination half-life approximately 4 hours) as compared to the (*R*)-enantiomer.

Absorption

NUVIGIL® is readily absorbed after oral administration. The absolute oral bioavailability was not determined due to the aqueous insolubility of armodafinil, which precluded intravenous administration.

Effect of Food

Food effect on oral bioavailability of Nuvigil is considered minimal; however, time to reach peak concentration (T_{max}) may be delayed by approximately 2-4 hours in the fed state. Since the delay in T_{max} is also associated with elevated plasma concentrations later in time, food can potentially effect the onset and time course of pharmacologic action for Nuvigil.

Distribution

NUVIGIL® has an apparent volume of distribution of approximately 42 L. Data specific to armodafinil protein binding are not available. However, modafinil is moderately bound to plasma protein (approximately 60%), mainly to albumin. The potential for interactions of NUVIGIL® with highly protein-bound drugs is considered to be minimal.

Metabolism

In vitro and *in vivo* data show that armodafinil undergoes hydrolytic deamidation, S-oxidation, and aromatic ring hydroxylation, with subsequent glucuronide conjugation of the hydroxylated products. Amide hydrolysis is the single most prominent metabolic pathway, with sulfone formation by cytochrome P450 (CYP) 3A4/5 being next in importance. The other oxidative products are formed too slowly *in vitro* to enable identification of the enzyme(s) responsible. Only two metabolites reach appreciable concentrations in plasma [i.e., (*R*)-modafinil acid and modafinil sulfone].

Data specific to NUVIGIL® disposition are not available. However, modafinil is mainly eliminated via metabolism, predominantly in the liver, with less than 10% of the parent compound excreted in the

urine. A total of 81% of the administered radioactivity was recovered in 11 days post-dose, predominantly in the urine (80% vs. 1.0% in the faeces).

Elimination

After oral administration of NUVIGIL®, armodafinil exhibits an apparent monoexponential decline from the peak plasma concentration. The apparent terminal $t_{½}$ is approximately 15 hours. The oral clearance of NUVIGIL® is approximately 33 mL/min.

Special Populations

Children

The pharmacokinetics of armodafinil have not been studied in children.

Age

In a clinical study, systemic exposure of armodafinil was approximately 15% higher in elderly subjects (≥65 years of age, N=24), corresponding to approximately 12% lower oral clearance (CL/F), as compared to young subjects (18-45 years of age, N=25). Systemic exposure of armodafinil acid (metabolite) was approximately 61% and 73% greater for C_{max} and $AUC_{0-τ}$, respectively, compared to young subjects. Systemic exposure of the sulfone metabolite was approximately 20% lower for elderly subjects compared with young subjects. A subgroup analysis of elderly subjects demonstrated elderly subjects ≥75 and 65-74 years of age had approximately 21% and 9% lower oral clearance, respectively, compared to young subjects. Systemic exposure was approximately 10% greater in subjects 65-74 years of age (N=17) and 27% greater in subjects ≥75 years of age (N=7), respectively, when compared to young subjects. The change is considered not likely to be clinically significant for elderly patients, however, because some elderly patients have greater exposure to armodafinil, consideration should be given to the use of lower doses.

Gender

Population pharmacokinetic analysis suggests no gender effect on the pharmacokinetics of armodafinil.

Race

The influence of race on the pharmacokinetics of armodafinil has not been studied.

Renal impairment

In a single dose 200 mg modafinil study, severe chronic renal failure (creatinine clearance ≤20 mL/min) did not significantly influence the pharmacokinetics of modafinil, but exposure to modafinil acid (metabolite) was increased 9 fold. There is inadequate information to determine safety and efficacy of NUVIGIL (armodafinil) dosing in patients with renal impairment, mild, moderate or severe.

Hepatic impairment

The oral clearance of modafinil was decreased by about 60% in patients with cirrhosis of the liver (Child-Pugh Class B or C) and the steady state concentration was doubled compared to normal patients. Therefore, the dose of NUVIGIL® should be reduced in patients with severe hepatic impairment (See DOSAGE AND ADMINISTRATION and PRECAUTIONS). There is a lack of data on dosing information for NUVIGIL (armodafinil) specific to the degree of liver impairment.

CLINICAL TRIALS

The effectiveness of NUVIGIL® in improving wakefulness has been established in the following sleep disorders: obstructive sleep apnoea/hypopnoea (OSAHS), narcolepsy and shift work sleep disorder (SWSD).

For each clinical trial, a p-value of ≤0.05 was required for statistical significance.

Obstructive Sleep Apnoea/hypopnoea (OSAHS)

The effectiveness of NUVIGIL® in improving wakefulness in patients with excessive sleepiness associated with OSAHS was established in two 12-week, multi-centre, placebo-controlled, parallel-group, double-blind studies of outpatients who met the International Classification of Sleep Disorders (ICSD) criteria for OSAHS (which are also consistent with the American Psychiatric Association DSM-IV-TR criteria). These criteria include either:

- excessive sleepiness or insomnia, plus frequent episodes of impaired breathing during sleep, and associated features such as loud snoring, morning headaches or dry mouth upon awakening; or
- excessive sleepiness or insomnia; and polysomnography demonstrating one of the following: more than five obstructive apnoeas, each greater than 10 seconds in duration, per hour of sleep; and one or more of the following: frequent arousals from sleep associated with the apnoeas, bradytachycardia, or arterial oxygen desaturation in association with the apnoeas.

In addition, for entry into these studies, all patients were required to have excessive sleepiness as demonstrated by a score ≥10 on the Epworth Sleepiness Scale, despite treatment with continuous positive airway pressure (CPAP). Evidence that CPAP was effective in reducing episodes of apnoea/hypopnoea was required along with documentation of CPAP use.

Patients were required to be compliant with CPAP, defined as CPAP use ≥4 hours/night on ≥70% of nights. CPAP use continued throughout the study. In both studies, the primary measures of effectiveness were 1) sleep latency, as assessed by the Maintenance of Wakefulness Test (MWT) and 2) the change in the patient's overall disease status, as measured by the Clinical Global Impression of Change (CGI-C) at the final visit. For a successful trial both measures had to show statistically significant improvement.

The MWT measures latency (in minutes) to sleep onset. An extended MWT was performed with test sessions at 2 hour intervals between 9AM and 7PM. The primary analysis was the average of the sleep latencies from the first four test sessions (9AM to 3PM). For each test session, the subject was asked to attempt to remain awake without using extraordinary measures. Each test session was terminated after 30 minutes if no sleep occurred or immediately after sleep onset. The CGI-C is a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse to Very Much Improved*. Evaluators were not given any specific guidance about the criteria they were to apply when rating patients.

In the first study 3021, a total of 395 patients with OSAHS were randomized to receive NUVIGIL® 150 mg/day, NUVIGIL® 250 mg/day or matching placebo. Patients treated with NUVIGIL® showed a statistically significant improvement in the ability to remain awake compared to placebo-treated patients as measured by the MWT at final visit. A statistically significant greater number of patients treated with NUVIGIL® showed improvement in overall clinical condition as rated by the CGI-C scale at final visit. The average sleep latencies (in minutes) in the MWT at baseline for the trials are shown in Table 1 below, along with the average change from baseline on the MWT at final visit. The percentages of patients who showed any degree of improvement on the CGI-C in the clinical trials are shown in Table 2 below. The two doses of NUVIGIL® produced statistically significant effects of similar magnitudes on the MWT, and also on the CGI-C.

In the second study 3025, 263 patients with OSAHS were randomized to either NUVIGIL® 150 mg/day or placebo. Patients treated with NUVIGIL® showed a statistically significant improvement in the ability to remain awake compared to placebo-treated patients as measured by the MWT (Table 1). A statistically significant greater number of patients treated with NUVIGIL® showed improvement in overall clinical condition as rated by the CGI-C scale (Table 2).

Night time sleep measured with polysomnography was not affected by the use of NUVIGIL® in either study.

Narcolepsy

The effectiveness of NUVIGIL® in improving wakefulness in patients with excessive sleepiness (ES) associated with narcolepsy was established in one 12-week, multi-centre, placebo-controlled, parallel-group, double-blind study of outpatients who met the ICSD criteria for narcolepsy. A total of 196 patients were randomized to receive NUVIGIL® 150 or 250 mg/day, or matching placebo. The ICSD criteria for narcolepsy include either:

- recurrent daytime naps or lapses into sleep that occur almost daily for at least three months, plus sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy), or
- a complaint of excessive sleepiness or sudden muscle weakness with associated features: sleep paralysis, hypnagogic hallucinations, automatic behaviours, disrupted major sleep episode; and polysomnography demonstrating one of the following: sleep latency less than 10 minutes or rapid eye movement (REM) sleep latency less than 20 minutes and a Multiple Sleep Latency Test (MSLT) that demonstrates a mean sleep latency of less than 5 minutes and two or more sleep onset REM periods and no medical or mental disorder accounts for the symptoms.

For entry into the study, all patients were required to have objectively documented excessive daytime sleepiness, via MSLT with a sleep latency of 6 minutes or less and the absence of any other clinically significant active medical or psychiatric disorder. The MSLT, an objective polysomnographic assessment of the patient's ability to fall asleep in an unstimulating environment, measured latency (in minutes) to sleep onset averaged over 4 test sessions at 2-hour intervals. For each test session, the subject was told to lie quietly and attempt to sleep. Each test session was terminated after 20 minutes if no sleep occurred or immediately after sleep onset.

The primary measures of effectiveness were: 1) sleep latency as assessed by the Maintenance of Wakefulness Test (MWT) and 2) the change in the patient's overall disease status, as measured by the CGI-C at the final visit. Each MWT test session was terminated after 20 minutes if no sleep occurred or immediately after onset in this study.

Patients treated with NUVIGIL® showed a statistically significantly enhanced ability to remain awake on the MWT at each dose compared to placebo at final visit (See Table 1). A statistically significant greater number of patients treated with NUVIGIL® at each dose showed improvement in overall clinical condition as rated by the CGI-C scale at final visit (Table 2).

The two doses of NUVIGIL® produced statistically significant effects of similar magnitudes on the CGI-C. Although a statistically significant effect on the MWT was observed for each dose, the magnitude of effect was observed to be greater for the higher dose.

Night time sleep measured with polysomnography was not affected by the use of NUVIGIL®.

Shift Work Sleep Disorder (SWSD)

The effectiveness of NUVIGIL® in improving wakefulness in patients with excessive sleepiness associated with SWSD was demonstrated in a 12-week, multi-centre, double-blind, placebo-controlled, parallel-group, clinical trial. A total of 254 patients with chronic SWSD were randomized to receive NUVIGIL® 150 mg/day or placebo. All patients met the ICSD criteria for chronic SWSD (which are consistent with the American Psychiatric Association DSM-IV-TR criteria for Circadian Rhythm Sleep Disorder: Shift Work Type). These criteria include: 1) either, a) a primary complaint of excessive sleepiness or insomnia which is temporally associated with a work period (usually night work) that occurs during the habitual sleep phase, or b) polysomnography and the MSLT demonstrate loss of a normal sleep-wake pattern (i.e., disturbed chronobiological rhythmicity); and 2) no other medical or mental disorder accounts for the symptoms; and 3) the symptoms do not meet criteria for any other sleep disorder producing insomnia or excessive sleepiness (e.g., time zone change [jet lag] syndrome).

It should be noted that not all patients with a complaint of sleepiness who are also engaged in shift work meet the criteria for the diagnosis of SWSD. In the clinical trial, only patients who were symptomatic for at least 3 months were enrolled.

Enrolled patients were also required to work a minimum of 5 night shifts per month, have excessive sleepiness at the time of their night shifts (MSLT score ≤6 minutes), and have daytime insomnia documented by a daytime polysomnogram (PSG).

The primary measures of effectiveness were 1) sleep latency, as assessed by the Multiple Sleep Latency Test (MSLT) performed during a simulated night shift at the final visit, and 2) the change in the patient's overall disease status, as measured by the CGI-C at the final visit.

Patients treated with NUVIGIL® showed a statistically significant prolongation in the time to sleep onset compared to placebo-treated patients, as measured by the night time MSLT at final visit (See Table 1). A statistically significant greater number of patients treated with NUVIGIL® showed improvement in overall clinical condition as rated by the CGI-C scale at final visit (See Table 2).

Daytime sleep measured with polysomnography was not affected by the use of NUVIGIL®.

Table 1 Average Baseline Sleep Latency and Change from Baseline at Final Visit (MWT and MSLT in minutes)

Disorder	Measure	NUVIGIL® 150 mg[a]		NUVIGIL® 250 mg[a]		Placebo	
		Baseline	Change from Baseline	Baseline	Change from Baseline	Baseline	Change from Baseline
OSAHS	MWT	21.5	1.7	23.3	2.2	23.2	-1.7
OSAHS	MWT	23.7	2.3	-	-	23.3	-1.3
Narcolepsy	MWT	12.1	1.3	9.5	2.6	12.5	-1.9
SWSD	MSLT	2.3	3.1	-	-	2.4	0.4

[a] Significantly different than placebo for all trials ($p<0.05$)

Table 2 Clinical Global Impression of Change (CGI-C) (Percentage of Patients Who Improved at Final Visit)

Disorder	NUVIGIL® 150 mg[a]	NUVIGIL® 250 mg[a]	Placebo
OSAHS	71%	74%	37%
OSAHS	71%	-	53%
Narcolepsy	69%	73%	33%
SWSD	79%	-	59%

[a] Significantly different than placebo for all trials ($p<0.05$)

INDICATIONS

NUVIGIL® is indicated:

- to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy;
- to treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where nonpharmacological interventions are unsuccessful or inappropriate;
- as an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.

CONTRAINDICATIONS

- Hypersensitivity to modafinil, armodafinil or any other component of the product.
- Use in pregnancy.

PRECAUTIONS

Armodafinil is a single enantiomer of racemic modafinil. The two enantiomers of modafinil have different pharmacokinetics. The half-life of armodafinil, the (*R*)-enantiomer, is approximately three times that of the (*S*)-enantiomer in adult humans. The implications of the pharmacokinetic differences between the drugs on the duration of clinical action remain unelucidated. No evidence of interconversion of the (*R*)- and (*S*)-enantiomers of modafinil have been observed *in vitro* or *in vivo*. Thus, armodafinil and modafinil are not bioequivalent, and therefore are not directly substitutable, (refer to Dosage and Administration).

Serious Rash, including Stevens-Johnson Syndrome

Serious rash requiring hospitalization and discontinuation of treatment has been reported in adults in association with the use of NUVIGIL® (armodafinil) and modafinil [the racemic mixture of (*S*)- and (*R*)-enantiomers].

NUVIGIL® has not been studied in paediatric patients in any setting and is not approved for use in paediatric patients for any indication.

In clinical trials of modafinil, the incidence of rash resulting in discontinuation was approximately 0.8% (13 per 1,585) in paediatric patients (age <17 years); these rashes included 1 case of possible Stevens-Johnson Syndrome (SJS) and 1 case of apparent multi-organ hypersensitivity reaction. Several of the cases were associated with fever and other abnormalities (e.g., vomiting, leukopenia). The median time to rash that resulted in discontinuation was 13 days. No such cases were observed among 380 paediatric patients who received placebo. No serious skin rashes have been reported in adult clinical trials (0 per 4,264) of modafinil. Rare cases of serious or life-threatening rash, including SJS, Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported in adults and children in worldwide post-marketing experience. The reporting rate of TEN and SJS associated with modafinil use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate. Estimates of the background incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years.

Cases of serious rash similar to those observed with modafinil including skin and mouth blistering have been reported in adults in post-marketing experience with NUVIGIL®.

There are no factors that are known to predict the risk of occurrence or the severity of rash associated with armodafinil or modafinil. Nearly all cases of serious rash associated with these drugs occurred within 1 to 5 weeks after treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g. 3 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes also occur with NUVIGIL®, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, NUVIGIL® should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

Angioedema and Anaphylactoid Reactions

Angioedema and hypersensitivity (with rash, dysphagia, and bronchospasm), were observed with NUVIGIL®. Patients should be advised to discontinue therapy and immediately report to their

physician any signs or symptoms suggesting angioedema or anaphylaxis (e.g., swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).

Multi-organ Hypersensitivity Reactions

Multi-organ hypersensitivity reactions, including at least one fatality in post marketing experience, have occurred in close temporal association (median time to detection 13 days: range 4-33) to the initiation of modafinil. A similar risk of multi-organ hypersensitivity reactions with armodafinil cannot be ruled out.

Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included myocarditis, hepatitis, liver function test abnormalities, haematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia. Because multi-organ hypersensitivity is variable in its expression, other organ system symptoms and signs, not noted here, may occur.

If a multi-organ hypersensitivity reaction is suspected, NUVIGIL® should be discontinued. Although there are no case reports to indicate cross-sensitivity with other drugs that produce this syndrome, the experience with drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

Persistent Sleepiness

Patients with abnormal levels of sleepiness who take NUVIGIL® should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking NUVIGIL®, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

Psychiatric Symptoms

In pre-approval narcolepsy, OSAHS and SWSD controlled trials of NUVIGIL®, anxiety, agitation, nervousness, and irritability were reasons for treatment discontinuation more often in patients on NUVIGIL® compared to placebo (NUVIGIL® 1.2% and placebo 0.3%). Depression was also a reason for treatment discontinuation more often in patients on NUVIGIL® compared to placebo (NUVIGIL® 0.6% and placebo 0.2%). Cases of suicide ideation were observed in clinical trials.

Caution should be exercised when NUVIGIL® is given to patients with a history of psychosis, depression, or mania. If psychiatric symptoms develop in association with NUVIGIL® administration, consider discontinuing NUVIGIL®.

Psychiatric adverse experiences have been reported in patients treated with modafinil. Modafinil and armodafinil (NUVIGIL®) are very closely related. Therefore, the incidence and type of psychiatric symptoms associated with NUVIGIL® are expected to be similar to the incidence and type of these events with modafinil.

Postmarketing adverse events associated with the use of modafinil have included mania, delusions, hallucinations, suicidal ideation and aggression, some resulting in hospitalization. Many, but not all, patients had a prior psychiatric history. One healthy 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.

Effects on Ability to Drive and Use of Machines

Although NUVIGIL® 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 NUVIGIL® therapy will not adversely affect their ability to engage in such activities.

Cardiovascular System

NUVIGIL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable angina, and such patients should be treated with caution.

In clinical studies of modafinil, cardiovascular adverse events, including chest pain, palpitations, dyspnoea 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 NUVIGIL® tablets not be used in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. Findings suggestive of mitral valve prolapse syndrome include, but are not limited to, ischemic ECG changes, chest pain, or arrhythmia. If new onset of any of these symptoms occurs, consider cardiac evaluation.

Blood pressure monitoring in short-term (≤3 months) pre-approval controlled trials of OSAHS, SWSD, and narcolepsy showed small average increases in mean systolic and diastolic blood pressure in patients receiving NUVIGIL® as compared to placebo (1.2 to 4.3 mmHg in the various experimental groups). There was also a slightly greater proportion of patients on NUVIGIL® requiring new or increased use of antihypertensive medications (2.9%) compared to patients on placebo (1.8%). There was a small, but consistent, average increase in pulse rate over placebo in pre-approval controlled trials. This increase varied from 0.9 to 3.5 BPM. Increased monitoring of heart rate and blood pressure may be appropriate in patients on NUVIGIL®. Caution should be exercised when prescribing NUVIGIL® to patients with known cardiovascular disease.

Patients (Women) Using Contraception

Sexually active women of child-bearing potential should be established on a contraceptive program before taking NUVIGIL®.

The effectiveness of steroidal contraceptives may be reduced when used with NUVIGIL® and for one month after discontinuation of therapy (See INTERACTIONS WITH OTHER MEDICINES). Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptive (e.g., Ethinylestradiol) when treated concomitantly with NUVIGIL® and for one month after discontinuation of NUVIGIL® treatment.

Genotoxicity

Armodafinil was negative in an *in vitro* bacterial reverse mutation assay and in an *in vitro* chromosomal aberration assay in human lymphocytes. Modafinil was negative in a series of *in vitro* (i.e., bacterial reverse mutation, mouse lymphoma tk, chromosomal aberration in human lymphocytes, cell transformation in BALB/3T3 mouse embryo cells) and *in vivo* (mouse bone marrow micronucleus) assays. These studies indicate that armodafinil has a low genotoxic potential.

Carcinogenicity

An oral carcinogenicity study conducted for 94-101 weeks in mice found no evidence of tumour development or neoplastic change in mice that received up to 300 mg/kg/day armodafinil in males, or up to 100 mg/kg/day in females. At the highest dose in mice the plasma armodafinil exposure (AUC) was similar in males (1.3x) and less in females (0.5x) than that in humans at the maximum recommended human dose (MRHD) of NUVIGIL®. Similarly, a carcinogenicity study which administered modafinil a mixture of (R)- and (S)- modafinil) to rats by the dietary route for 104 weeks at oral doses of 6, 30 and 60 mg/kg/day found no evidence of tumorigenesis associated with modafinil

administration. However, minimal toxicity was observed in the high dose group. These results indicate that the exposure of armodafinil or modafinil was insufficient to adequately assess carcinogenic potential.

Effects on fertility

A fertility and early embryonic development (to implantation) study was not conducted with armodafinil alone.

Oral administration of modafinil (doses of up to 480 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through day 7 of gestation (implantation) had no adverse effect on fertility or reproductive parameters, apart from an increase in time to mate at the highest dose. The no-effect dose for effects on fertility of 480 mg/kg/day was associated with a modafinil exposure (plasma AUC) about twice that in humans at the MHRD.

Use in Pregnancy (Category B3)

Modafinil and/or its metabolites cross the placenta in rats, but placental transfer of armodafinil *per* se has not been studied. In studies of armodafinil [(*R*)-modafinil] and modafinil [a mixture of (*R*)- and (*S*)-modafinil] conducted in rats (armodafinil, modafinil) and rabbits (modafinil), developmental toxicity was observed at clinically relevant plasma exposures.

Oral administration of armodafinil (60, 200, or 600 mg/kg/day) to pregnant rats throughout organogenesis resulted in increased incidences of fetal visceral and skeletal variations and decreased fetal body weights at the highest dose. The highest no-effect dose for embryofetal developmental toxicity in rat was associated with a plasma armodafinil exposure (AUC) less than that in humans at the MRHD of NUVIGIL® (250 mg/day).

Similarly, modafinil (50, 100, or 200 mg/kg/day) administered orally to pregnant rats throughout organogenesis caused, in the absence of maternal toxicity, an increase in resorptions and an increased incidence of visceral and skeletal variations in the offspring at the highest dose tested. The higher no-effect dose for embryofetal developmental toxicity in rats (100 mg/kg/day) was associated with a plasma armodafinil AUC less than that in humans at the MRHD of NUVIGIL®. In a subsequent study of up to 480 mg/kg/day of modafinil, no adverse effects on embryofetal development were observed.

In pregnant rabbits, the incidences of fetal structural alterations and embryofetal death were increased at the highest dose of 180 mg/kg/day modafinil. At the highest no-effect dose for developmental toxicity, plasma armodafinil AUC was less than that in humans at the MRHD of NUVIGIL®.

Modafinil administration to rats throughout gestation and lactation at oral doses of up to 200 mg/kg/day resulted in decreased viability in the offspring at doses greater than 20 mg/kg/day, a dose associated with plasma armodafinil AUC less than that in humans at the MRHD of NUVIGIL®. No effects on postnatal developmental and neurobehavioral parameters were observed in surviving offspring.

As there are no adequate and well-controlled trials with NUVIGIL® in pregnant women, it should be contraindicated during pregnancy. Intrauterine growth restriction and spontaneous abortion has been reported in association with armodafinil and modafinil in humans. Whether the cases reported with armodafinil are drug related is unknown.

Patients should be cautioned regarding the potential increased risk of pregnancy when using steroidal contraceptives with NUVIGIL® and for one month after discontinuation of therapy (See INTERACTIONS WITH OTHER MEDICINES).

Use in Lactation

It is not known whether armodafinil or its metabolites are excreted in human milk. Modafinil and/or its metabolites including modafinil sulfone and modafinil acid have been found in the milk of lactating rats. Breastfeeding is not recommended during administration of NUVIGIL®.

Abuse and Dependence Potential

Although the abuse potential of armodafinil has not been specifically studied, its abuse potential is likely to be similar to that of modafinil.

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 behaviour).

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).

Effect on laboratory tests

Clinical chemistry, haematology, and urinalysis parameters were monitored in the studies. Mean plasma levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (AP) were found to be higher following administration of NUVIGIL®, but not placebo. Few subjects, however, had GGT or AP elevations outside of the normal range. No differences were apparent in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, or total bilirubin, although there were rare cases of isolated elevations of AST and/or ALT. A single case of mild pancytopenia was observed after 35-days of treatment and resolved with drug discontinuation. A small mean decrease from baseline in serum uric acid compared to placebo was seen in clinical trials. The clinical significance of this finding is unknown.

Paediatric Use

There is a lack of either safety or efficacy data for use in paediatric populations (See Serious Rash, including Stevens-Johnson Syndrome). Serious rash has been seen in paediatric patients receiving modafinil.

Hepatic Impairment

The dose of NUVIGIL® should be reduced in patients with severe hepatic impairment, with or without cirrhosis (See PHARMACOLOGY and DOSAGE AND ADMINISTRATION). There is a lack of data on dosing instruction for NUVIGIL (armodafinil) specific to the degree of liver impairment.

Renal Impairment

There is inadequate information to determine safety and efficacy of NUVIGIL (armodafinil) dosing in patients with renal impairment, mild, moderate or severe. (See PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Use in the Elderly

In elderly patients, elimination of armodafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses and close monitoring in this population (See DOSAGE AND ADMINISTRATION).

INTERACTIONS WITH OTHER MEDICINES

In vitro data demonstrated that armodafinil weakly induces CYP1A2 and possibly CYP3A activities in a concentration-related manner and that CYP2C19 activity is reversibly inhibited by armodafinil. *In vivo*, CYP2B6 was induced by armodafinil. Other CYP activities did not appear to be affected by armodafinil. An *in vitro* study demonstrated that armodafinil is a substrate of P-glycoprotein.

Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P450 Isoenzymes and Other Hepatic Enzymes

The existence of multiple pathways for armodafinil metabolism, as well as the fact that a non-CYP-related pathway is the most rapid in metabolizing armodafinil, suggest that there is a low probability of substantive effects on the overall pharmacokinetic profile of NUVIGIL® due to CYP inhibition by concomitant medications. However, due to the partial involvement of CYP3A enzymes in the metabolic elimination of armodafinil, co-administration of potent inducers of CYP3A4/5 (e.g., carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin and St. John's Wort) or inhibitors of CYP3A4/5 (e.g., protease inhibitors; ritonavir, indinavir, nelfinavir, saquinavir; clarithromycin, erythromycin chloramphenicol, ketoconazole,itraconazole, nefazodone, diltiazem and verapimil) could alter the plasma concentrations of armodafinil.

The Potential of NUVIGIL® to Alter the Metabolism of Other Drugs by Enzyme Induction or Inhibition

Drugs Metabolized by CYP3A4/5
In vitro data demonstrated that the armodafinil metabolite modafinil sulfone, is a weak inducer of CYP3A activity. In a clinical study, concomitant administration of NUVIGIL® 250 mg resulted in a reduction in systemic exposure to midazolam by 32% after a single oral dose (5 mg) and 17% after a single intravenous dose (2 mg). Therefore, the blood levels and effectiveness of drugs that are substrates for CYP3A enzymes (e.g., steroidal contraceptives, cyclosporine, midazolam, and triazolam) may be reduced after initiation of concomitant treatment with NUVIGIL®, and dose adjustment may be required.

In a clinical study the concomitant administration of NUVIGIL® 250 mg with carbamazepine (400 mg/day) resulted in a reduction in the mean systemic exposure of carbamazepine by approximately 25%. Carbamazepine dose adjustment may be required when coadministered with NUVIGIL®, particularly when starting or stopping coadministration of the two drugs.

In a separate clinical study, concomitant administration of NUVIGIL® 250 mg with quetiapine (300 mg to 600 mg daily doses) resulted in a reduction in the mean systemic exposure of quetiapine by approximately 29%. No dose adjustment is required.

The blood levels of cyclosporine may be reduced when used with NUVIGIL®. Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustment for cyclosporine should be considered when these drugs are used concomitantly.

Drugs Metabolized by CYP1A2
In vitro data demonstrated that armodafinil and its metabolite modafinil sulfone are weak inducers of CYP1A2 in a concentration-related manner. However, in a clinical study using caffeine as a probe substrate, no significant effect on CYP1A2 activity was observed.

Drugs Metabolized by CYP2C19
In vitro data demonstrated that armodafinil, and more so its metabolite modafinil sulfone, are reversible inhibitors of CYP2C19 activity. In a clinical study, concomitant administration of NUVIGIL® 400 mg resulted in a 40% increase in exposure to omeprazole after a single oral dose (40 mg), as a result of moderate inhibition of CYP2C19 activity. Therefore, dose reduction may be required for some drugs that are substrates for CYP2C19 (e.g., phenytoin, diazepam, propranolol, omeprazole, esomeprazole, and clomipramine) when used concomitantly with NUVIGIL®.

Drugs Metabolized by CYP2B6

In vitro data demonstrated that racemic modafinil is a weak inducer of CYP2B6 activity in a concentration-related manner.

Interactions with CNS Active Drugs

Concomitant administration of NUVIGIL® with quetiapine reduced the systemic exposure of quetiapine.

Data specific to NUVIGIL® drug-drug interaction potential with other CNS active drugs are not available. However, the following available drug-drug interaction information on modafinil should be applicable to NUVIGIL®.

Concomitant administration of modafinil with methylphenidate or dextroamphetamine produced no significant alterations on the pharmacokinetic profile of modafinil or either stimulant, even though the absorption of modafinil was delayed for approximately one hour.

Concomitant modafinil or clomipramine did not alter the pharmacokinetic profile of either drug; however, one incident of increased levels of clomipramine and its active metabolite desmethylclomipramine was reported in a patient with narcolepsy during treatment with modafinil.

Data specific to NUVIGIL® or modafinil drug-drug interaction potential with monoamine oxidase (MAO) inhibitors are not available. Therefore, caution should be used when concomitantly administering MAO inhibitors and NUVIGIL®.

Interaction with P-Glycoprotein

An *in vitro* study demonstrated that armodafinil is a substrate, but not inhibitor, of P-glycoprotein. The clinical impact of inhibition of P-glycoprotein on the bioavailability of armodafinil is not known.

Interactions with Other Drugs

Data specific to NUVIGIL® drug-drug interaction potential for additional other drugs are not available. However, the following available drug-drug interaction information on modafinil should be applicable to NUVIGIL®.

Concomitant administration of modafinil with warfarin did not produce significant changes in the pharmacokinetic profiles of (*R*)- and (*S*)-warfarin. However, since only a single dose of warfarin was tested in this study, an interaction cannot be ruled out. Therefore, more frequent monitoring of prothrombin times/INR should be considered whenever NUVIGIL® is coadministered with warfarin.

ADVERSE EFFECTS

OSAHS, SWSD, and Narcolepsy

NUVIGIL® has been evaluated for safety in over 1100 patients with excessive sleepiness associated with OSAHS, SWSD and narcolepsy.

In the pre-approval controlled clinical trials, the most commonly observed adverse events (≥5%) associated with the use of NUVIGIL® occurring more frequently than in the placebo-treated patients were headache, nausea, dizziness, and insomnia. The adverse event profile was similar across the studies.

In the pre-approval controlled clinical trials, 44 of the 645 patients (7%) who received NUVIGIL® discontinued due to an adverse experience compared to 16 of the 445 (4%) of patients that received placebo. The most frequent reason for discontinuation was headache (1%).

Incidence in Controlled Trials

The following table (Table 3) presents the adverse experiences that occurred at a rate of 1% or more and were more frequent in patients treated with NUVIGIL® than in placebo group patients in the pre-approval 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 3 Incidence 1% or Greater Of Treatment-Emergent Adverse Experiences In Parallel-Group, Placebo-Controlled Clinical Trials* In OSAHS, Narcolepsy and SWSD With NUVIGIL® (150 mg and 250 mg)[1]

System Organ Class MeDRA preferred term	Nuvigil® (percent, N=645)	Placebo (percent, N=445)
Cardiac Disorders		
Palpitations	2	1
Gastrointestinal Disorders		
Nausea	7	3
Diarrhoea	4	2
Dry Mouth	4	1
Dyspepsia	2	0
Abdominal Pain Upper	2	1
Constipation	1	0
Vomiting	1	0
Loose Stools	1	0
General Disorders and Administration Site Conditions		
Fatigue	2	1
Thirst	1	0
Influenza-like Illness	1	0
Pain	1	0
Pyrexia	1	0
Immune System Disorders		
Seasonal Allergy	1	0
Investigations		
Gamma-Glutamyltransferase Increased	1	0
Heart Rate Increased	1	0
Metabolism and Nutritional Disorders		
Anorexia	1	0
Decreased Appetite	1	0
Nervous System Disorders		
Headache	17	9
Dizziness	5	2
Disturbance in Attention	1	0
Tremor	1	0
Migraine	1	0
Paresthesia	1	0
Psychiatric Disorders		
Insomnia	5	1
Anxiety	4	1
Depression	2	0
Agitation	1	0
Nervousness	1	0
Depressed Mood	1	0
Renal and Urinary Disorders		
Polyuria	1	0
Respiratory, Thoratic and Mediastinal Disorders		
Dyspnea	1	0
Skin and Subcutaneous Tissue Disorders		
Rash	2	0
Contact Dermatitis	1	0
Hyperhydrosis	1	0

* Four double-blind, placebo-controlled clinical studies in SWSD, OSAHS and narcolepsy; incidence is rounded to the nearest whole percent. Included are only those events for which NUVIGIL® incidence is greater than that of placebo.
1. Events for which the NUVIGIL® incidence was at least 1% but equal to or less than placebo are not listed in the table. The events included the following: flatulence, chest pain, bronchitis, nasopharyngitis, sinusitis, upper respiratory tract infection, alanine aminotransferase increased, aspartate aminotransferase increased, arthralgia, back pain, oropharyngeal pain, cough and hypertension.

Dose Dependency of Adverse Events

In the pre-approval controlled clinical trials which compared doses of 150 mg/day and 250 mg/day of NUVIGIL and placebo, the only adverse events that appeared to be dose-related were headache, rash, depression, dry mouth, insomnia, and nausea. See Table 4 for additional information.

Table 4. Incidence Of Dose-Dependent, Treatment-Emergent Adverse Experiences By Dose and By Treatment In Parallel-Group, Placebo-Controlled Clinical Trials* In OSAHS, Narcolepsy and SWSD With NUVIGIL® (150 mg and 250 mg)

System Organ Class MedDRA preferred term	NUVIGIL® 250 mg (%) N=198	NUVIGIL® 150 mg (%) N=447	NUVIGIL® Combined (%) N=645	Placebo (%) N=445
Gastrointestinal Disorders				
Nausea	9	6	7	3
Dry Mouth	7	2	4	<1
Nervous System Disorders				
Headache	23	14	17	9
Psychiatric Disorders				
Insomnia	6	4	5	1
Depression	3	1	2	<1
Skin And Subcutaneous Tissue Disorders				
Rash	4	1	2	<1

* Four double-blind, placebo-controlled clinical studies in SWSD, OSAHS, and narcolepsy.

Vital Sign Changes

Blood pressure monitoring in pre-approval controlled trials of OSAHS, SWSD, and narcolepsy showed small average increases in mean systolic and diastolic blood pressure in patients receiving NUVIGIL® as compared to placebo (1.2 to 4.3 mmHg in the various experimental groups). There was also a slightly greater proportion of patients on NUVIGIL® requiring new or increased use of antihypertensive medications (2.9%) compared to patients on placebo (1.8%). There was a small, but consistent, average increase in pulse rate over placebo in pre-approval controlled trials. This increase varied from 0.9 to 3.5 BPM.

Post Marketing Experience

Post Marketing Experience for NUVIGIL®, principally from spontaneous reporting based on reporting rates and not incidence rates, has documented the following adverse events.

Common 1/100 to <1/10
Uncommon 1/1,000 to <1/100
Rare 1/10,000 to <1/1,000
Very rare <1/10,000

Cardiac disorders
Very rare Supraventricular arrhythmias, myocardial infarction

General disorders
Rare Feeling abnormal, irritability

Immune system disorders
Very rare Drug hypersensitivity, anaphylaxis
Nervous system disorders
Very rare Convulsions

Psychiatric disorders
Very rare Hallucination, anger, aggression, drug abuse, psychotic disorder, suicidal ideation, suicide attempt

Respiratory, thoracic and mediastinal disorders
Very rare Throat tightness, pharyngeal oedema

Skin and subcutaneous tissue disorders
Very rare Stevens-Johnson syndrome, alopecia

DOSAGE AND ADMINISTRATION

NUVIGIL® should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of the underlying disorder of narcolepsy, OSAHS, or SWSD has been made in accordance with ICSD or DSM diagnostic criteria. Such an evaluation usually consists of a complete history and physical examination, and it may be supplemented with testing in a laboratory setting. Some patients may have more than one sleep disorder contributing to their excessive sleepiness (e.g., OSAHS and SWSD coincident in the same patient).

NUVIGIL® may be taken with or without food, however administration with food may delay the onset of action and prolong the effect of the drug (See Pharmacokinetics/Absorption/Effects of Food).

To avoid a delayed onset of action NUVIGIL should be taken on an empty stomach.

Treatment with NUVIGIL® should be initiated and supervised by physicians with appropriate experience in the treatment of sleep disorders who have access to sleep laboratory diagnostic facilities.

Narcolepsy

The recommended dose of NUVIGIL® for patients with narcolepsy is 150 mg or 250 mg given once daily in the morning.

Obstructive Sleep Apnoea/Hypopnoea Syndrome (OSAHS)

In OSAHS, NUVIGIL® is not indicated as treatment for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating NUVIGIL® for excessive sleepiness. If NUVIGIL® is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary. There was a slight trend for reduced CPAP use over time (mean reduction of 18 minutes for patients treated with NUVIGIL® and a 6-minute reduction for placebo-treated patients from a mean baseline use of 6.9 hours per night) in NUVIGIL® trials.

The recommended dose of NUVIGIL® for patients with OSAHS is 150 mg or 250 mg given once daily in the morning. In patients with OSAHS, doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that these doses confer additional benefit beyond that of the 150 mg/day dose (See CLINICAL TRIALS).

Shift Work Sleep Disorder (SWSD)

The recommended dose of NUVIGIL® for patients with SWSD is 150 mg given daily approximately 1 hour prior to the start of their work shift.

Dosing in Special Populations

The dose of NUVIGIL should be reduced in patients with severe hepatic impairment, with or without cirrhosis (See SPECIAL POPULATIONS). There is a lack of data on dosing instruction for NUVIGIL (armodafinl) specific to the degree of liver impairment.

There is inadequate information to determine safety and efficacy of dosing of NUVIGIL (armodafinil) in patients with renal impairment, mild, moderate or severe (See SPECIAL POPULATIONS).

In elderly patients, elimination of armodafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses in this population (See SPECIAL POPULATIONS).

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26.

There were no overdoses reported in the NUVIGIL® clinical studies. Symptoms of NUVIGIL® overdose are likely to be similar to those of modafinil. Symptoms of overdose in modafinil clinical trials included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters.

From post-marketing experience with modafinil, 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, agitation, anxiety, excitation and hallucination; digestive changes such as nausea and diarrhoea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain.

No specific antidote exists for the toxic effects of a NUVIGIL® overdose. Such overdoses should be managed with primarily supportive care, including cardiovascular monitoring. There are no data to suggest the utility of dialysis or urinary acidification or alkalinization in enhancing drug elimination.

PRESENTATION AND STORAGE CONDITIONS

50 mg: Each round, white to off-white tablet is debossed with  on one side and “205” on the other. Bottles of 30

150 mg: Each oval, white to off-white tablet is debossed with  on one side and “215” on the other. Bottles of 30

250 mg: Each oval, white to off-white tablet is debossed with  on one side and “225” on the other. Bottles of 30

All strengths of armodafinil tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant polypropylene closures and sealed with an induction inner seal.

The 150 mg and 250 mg strengths are also available in PVC blisters sealed to an aluminium foil lidding (physician’s sample pack only).

Store below 25°C.

Protect from light.

Protect from moisture.

NAME AND ADDRESS OF SPONSOR

Teva Pharmaceuticals Australia Pty Ltd.
Level 2, 37 Epping Road
Macquarie Park
NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS:

26 November 2015

DATE OF MOST RECENT AMENDMENT: