

PRODUCT INFORMATION

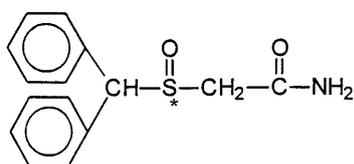
MODAVIGIL® (modafinil)

PRODUCT INFORMATION

NAME OF THE MEDICINE

Modavigil (modafinil).

MODAVIGIL® (modafinil) is a wakefulness-promoting agent for oral administration. Modafinil is a racemic compound and the chemical name is 2-[(diphenylmethyl)sulfinyl] acetamide. The molecular formula is C₁₅H₁₅NO₂S and the molecular weight is 273.35. The chemical structure is:



* chiral centre

The CAS registry number is 68693-11-8.

DESCRIPTION

Modafinil is a white to off-white, crystalline powder that is practically insoluble in water and cyclohexane. It is sparingly to slightly soluble in ethanol and acetone. Each MODAVIGIL® tablet contains 100 mg of modafinil and also lactose, pregelatinised maize starch, microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

The precise mechanism(s) through which modafinil promotes wakefulness is unknown. Modafinil has wake-promoting actions but a pharmacological profile that is distinct from sympathomimetic amines, which increase wakefulness by other mechanisms.

Modafinil does not bind to most of the potentially relevant receptors for sleep/wake regulation, including those for noradrenaline, serotonin, dopamine, GABA, adenosine, histamine-3 and benzodiazepines. Modafinil is not a direct- or indirect-acting dopamine receptor agonist and is inactive in several *in vivo* preclinical models capable of detecting enhanced dopaminergic activity. *In vitro*, modafinil binds to the dopamine reuptake site with low affinity and causes an increase in extracellular dopamine, but no increase in dopamine release. Modafinil does not appear to be a direct or indirect α_1 -adrenergic agonist. Although modafinil-induced wakefulness can be attenuated by the α_1 -adrenergic receptor antagonist prazosin, modafinil has no activity in assay systems known to be responsive to the α -adrenergic agonists.

In rats, the wakefulness induced by amphetamine, but not modafinil, was antagonised by the dopamine receptor antagonist haloperidol. In cats, modafinil evoked neuronal activation in brain regions different from methylphenidate and amphetamine. Modafinil served as a positive reinforcer for cocaine in monkeys and was partially discriminated as stimulant-like in rats (see “**PRECAUTIONS, Dependence Potential**”).

The optical enantiomers of modafinil have similar pharmacological actions in mice, but have not been studied individually in humans. The two major metabolites of modafinil, modafinil acid and modafinil sulfone, showed little CNS-activating activity in animal studies.

Modafinil in humans restores and/or improves the level of wakefulness. Changes are found in electrophysiological parameters reflecting alertness (ratio of power of alpha rhythm to power of theta rhythm), starting from a dose of 100 mg in the morning. An increase is seen in latency periods in the multiple sleep latency test, starting from 200 mg in the morning. Modafinil opposes the impairment of cognitive (in particular, memory), psychomotor and neurosensory performance induced by sleep deprivation. This activity is observed in the absence of any modifications of appetite or behaviour.

Morning administration of 200 mg does not appear to affect nocturnal sleep. Administration of 100 mg morning and noon may prolong the subjective time taken to fall asleep. Evening administration may disturb sleep. This pharmacodynamic activity does not appear to affect the autonomic nervous system.

Pharmacokinetics

Modafinil is a racemic compound, whose enantiomers have different pharmacokinetics (eg. the half-life of the *l*-isomer is approximately three times that of the *d*-isomer in humans). The enantiomers do not interconvert. At steady state, total exposure to the *l*-isomer is approximately three times that of the *d*-isomer. The trough concentration (C_{minss}) of circulating modafinil after once daily dosing consists of 90% of the *l*-isomer and 10% of the *d*-isomer.

Absorption and Distribution

Modafinil is slowly absorbed with an absorption half-life of approximately 1 hour. Peak plasma concentrations (C_{max}) of approximately 3.3mg/L are reached 3 hours (t_{max}) after administration of a 200 mg dose. Both the area under the plasma concentration curve (AUC), and the peak plasma concentration show dose-proportionality in the 50 to 400 mg range. The absolute oral bioavailability could not be determined due to the aqueous insolubility (< 1mg/mL) of modafinil, which precluded intravenous administration. Food has no effect on the overall bioavailability of modafinil, however, its absorption (t_{max}) may be delayed by approximately one hour if taken with food.

Modafinil is well distributed in body tissue with an apparent volume of distribution (~0.9 L/kg) larger than the volume of total body water (0.6 L/kg). Modafinil is weakly

bound to plasma proteins (62%), mainly to albumin. At serum concentrations obtained at steady state after doses of 200 mg/day, modafinil exhibits no displacement of protein binding of warfarin, diazepam, or propranolol.

Metabolism and Excretion

The major route of elimination (~90%) is metabolism, primarily by the liver, with subsequent renal elimination of the metabolites. The elimination half-life of modafinil after multiple doses is about 10-12 hours. Urine alkalinisation has no effect on the elimination of modafinil.

Metabolism occurs through hydrolytic deamination, S-oxidation, aromatic ring hydroxylation, and glucuronide conjugation. Less than 10% of an administered dose is excreted as the parent compound. In a clinical study using radiolabelled modafinil, a total of 81% of the administered radioactivity was recovered in 11 days post-dose, predominantly in the urine (80% vs. 1% in the faeces).

The chief metabolite (40-50% of the dose) is acid modafinil, which has no pharmacological activity. The excretion of modafinil and its metabolites is chiefly renal, with a small proportion being eliminated unchanged (< 10%).

Only two metabolites reach appreciable concentrations in plasma, i.e., acid modafinil and modafinil sulfone. In preclinical models, modafinil acid, modafinil sulfone, 2-[(diphenylmethyl)sulfonyl]acetic acid and 4-hydroxy modafinil, were inactive or did not appear to mediate the arousal effects of modafinil.

In humans, modafinil shows a possible induction effect on its own metabolism after chronic administration of doses \geq 400 mg/day. *In vitro* studies with human hepatocytes and liver microsomes have shown induction of metabolising enzymes CYP3A4 and CYP1A1/2, and inhibition of CYP2C19 (see "**PRECAUTIONS, Interaction with Other Drugs**").

Special Populations

Children: The pharmacokinetics of modafinil have not been studied in children.

Age effect: A slight decrease (~20%) in the oral clearance of modafinil was observed in subjects with a mean age of 63 years (range: 53 to 73 years). The clearance of modafinil may be reduced in the elderly.

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

Race effect: The influence of race on the pharmacokinetics of modafinil has not been studied.

Renal impairment: The pharmacokinetics of modafinil were not significantly influenced in patients with severe chronic renal failure (creatinine clearance \leq 20mL/min), but the exposure to modafinil acid (an inactive metabolite) was increased 9 fold.

Hepatic impairment: The oral clearance of modafinil was decreased by about 60% and the steady state concentration was doubled in patients with severe chronic hepatic impairment.

CLINICAL TRIALS

Studies reported here were multicenter, randomized, double-blind, placebo-controlled parallel-group clinical trials. The efficacy criteria reported for the trials included:

- Maintenance of Wakefulness Test (MWT), which quantitatively measures the patient's ability to resist sleep and maintain wakefulness. The patients were asked to attempt to remain awake without using extraordinary measures. The test was terminated after 20 minutes if no sleep occurred or 10 minutes after sleep onset.
- Clinical Global Impression of Change (CGI-C), which is a 7-point scale ranging from "Very Much Worse" to "Very Much Improved" from baseline; it was assessed by an independent clinician who had no access to any data about the patients other than a measure of their baseline severity.
- Epworth Sleepiness Scale (ESS), which is a recall-based questionnaire devised to provide a measurement of the subject's general level of day-to-day sleepiness, or preferably, sleep propensity.

Narcolepsy:

The effectiveness of MODAVIGIL® in reducing the excessive sleepiness (ES) associated with narcolepsy was established in two US 9-week, multicentre, placebo-controlled, two-dose (200mg per day and 400mg per day) parallel-group, double-blind studies of outpatients who met the ICD-9 and American Sleep Disorders Association criteria for narcolepsy (which are also consistent with the American Psychiatric Association DSM-IV criteria). These criteria 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.

In addition, for entry into these studies, all patients were required to have objectively documented excessive daytime sleepiness, a Multiple Sleep Latency Test with two or more sleep onset REM periods, and the absence of any clinically significant active medical or psychiatric disorder.

In both studies, the primary measures of effectiveness were 1) sleep latency, as assessed by the MWT and 2) the change in the patient's overall disease status, as measured by the CGI-C. For a successful trial, both measures had to show significant improvement.

Patients in both MODAVIGIL[®] treatment groups were able to stay awake longer than those receiving placebo, and were rated by an independent clinician as having a significant improvement in illness. A statistically significantly enhanced ability to remain awake was shown on the MWT and the CGI-C scale (see Tables 1 and 2).

Obstructive Sleep Apnoea/Hypopnoea Syndrome (OSAHS):

The results from two major phase 3 clinical trials of modafinil in patients with OSAHS are presented in Tables 1 and 2. The effectiveness of MODAVIGIL[®] in reducing the excessive sleepiness associated with OSAHS was established in two clinical trials. In both studies, patients were enrolled who met the International Classification of Sleep Disorders (ICSD) criteria for OSAHS (which are also consistent with the American Psychiatric Association DSM-IV criteria). These criteria include either, 1) excessive sleepiness or insomnia, plus frequent episodes of impaired breathing during sleep, and associated features such as loud snoring, morning headaches and dry mouth upon awakening; or 2) 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, bradycardia, and 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/hypopnea was required along with documentation of CPAP use.

Study 303 (n = 327) assessed the efficacy and safety of two doses of modafinil (200 mg and 400 mg per day) in the treatment of excessive sleepiness in patients with established OSAHS, despite partial or satisfactory use of continuous positive airway pressure (CPAP) therapy. The primary efficacy variables for study 303 were MWT and CGI-C. Study 402 (n = 157) provides supportive data for modafinil 400mg per day in the treatment of excessive sleepiness in patients with established OSAHS, despite the use of effective CPAP therapy. The primary efficacy variable for study 402 was ESS.

Clinically significant improvements were reported for each parameter and for both doses of modafinil compared to placebo in Study 303 out to 12 weeks' double-blind treatment, and Study 402 out to 4 weeks' double-blind treatment (see Tables 1 and 2).

In a 12 month open-label extension period for Study 303 in which patients titrated their daily dose of modafinil according to clinical response, ESS scores remained consistently improved compared to baseline values in both those previously on modafinil and those previously on placebo.

For OSAHS, modafinil has been shown to produce clinically meaningful reductions in excessive sleepiness and its adverse effects on quality of life, in both the short and long term.

Shift Work Sleep Disorder (SWSD):

Two clinical trials conducted in patients with shift work sleep disorder provide information on the efficacy of modafinil in this indication. The moderate to severe subgroup of patients with SWSD for whom Modavigil is indicated is defined by the inclusion criteria in the pivotal clinical trials. These criteria included a CGI-S (Clinical Global Impression of Severity) rating of at least “moderately ill” (relating to ES on shift nights) at baseline, a mean sleep latency of no more than 6 minutes on the Multiple Sleep Latency Test (MSLT) and no more than 87.5% sleep efficiency (time sleeping/time in bed).

All patients met the International Classification of Sleep Disorders (ICSD-10) criteria for chronic SWSD (which are consistent with the American Psychiatric Association DSM-IV criteria for Circadian Rhythm Sleep Disorder: Shift Work Type). Patients were enrolled if they worked at least 5 night shifts per month (of which at least 3 nights were consecutive) and planned to maintain this schedule for the duration of the double-blind portion of the study. Each night shift was no longer than 12 hours in duration and included at least 6 hours between the hours of 2200 and 0800. Patients with any other disorder that might account for their excessive sleepiness were excluded.

Placebo or modafinil was taken 30 to 60 minutes before each night shift. Having worked three consecutive night shifts, patients were admitted to the sleep centre for a fourth, simulated night shift (= a study visit), during which the various efficacy parameters were assessed.

Study 305 (n = 209) evaluated the efficacy and safety of 12 weeks’ therapy with modafinil at a dose of 200 mg as treatment for adults with excessive sleepiness associated with chronic shift work sleep disorder. The primary efficacy variables were MSL-MSLT and CGI-C. Statistically significant improvements were seen for patients in the modafinil group when compared to patients in the placebo group for both of the primary endpoint measures (see Tables 1 and 3).

Study 306 (n = 278) evaluated the safety and impact on Quality of Life of 12 weeks of modafinil therapy at dosages of 200 or 300mg once daily as treatment for adults with excessive sleepiness associated with shift work sleep disorder. The potential impact of modafinil treatment on quality-of-life was assessed by measuring the mean changes from baseline to week 12 using the following measures:

- Functional Outcomes of Sleep Questionnaire (FOSQ)
- 36-Item Short Form Health Survey (SF-36)

In Study 306, modafinil treatment appeared to have a clinically meaningful effect on patient quality of life as assessed by the FOSQ. For the patients in the modafinil 300 mg/day group, improvement from baseline to week 12 was statistically significant for the total score (p = 0.0126), and for the individual scores for vigilance (p = 0.0123),

activity level ($p = 0.0055$) and general productivity ($p = 0.0041$) when compared with placebo. Although not statistically significant, the p-values for the change from baseline for the modafinil-200mg/day treatment group showed a trend toward significance.

Improvement was observed in the mental component score of SF-36 at all time points for patients in the modafinil-treated groups compared with the placebo-treated group. Statistical significance was observed at endpoint with the modafinil 300 mg/day group for the mental component summary ($p = 0.0113$), vitality ($p < 0.0001$) and role emotion ($p = 0.0444$) when compared with placebo.

In a 12-month open label extension period for Study 306, improvements in FOSQ total score and in the SF-36 mental composite score at endpoint were of the same magnitude as those seen in the double-blind period, and were considered clinically meaningful.

In SWSD, modafinil has been shown to produce clinically meaningful reductions in excessive sleepiness and had positive impact on quality of life, in both the short and long term.

Table 1. Summary of the pivotal US clinical studies of MODAVIGIL® as measured by defined CGI-C responder rates

	Study	400 mg	200 mg	Placebo
CGI-C number (%) improved at end-point	Narcolepsy Study 301	62 (72)	61 (64)	34 (37)
p-values compared to placebo		<i>p</i> = 0.0001	<i>p</i> = 0.0001	not applicable
CGI-C number (%) improved at end-point	Narcolepsy Study 302	52 (60)	48 (58)	33 (38)
p-values compared to placebo		<i>p</i> = 0.0026	<i>p</i> = 0.0044	not applicable
CGI-C number (%) improved at end-point	OSAHS Study 303	63 (68%)	60 (61%)	37 (37%)
p-values compared to placebo		<i>p</i> = 0.0001	<i>p</i> = 0.0009	not applicable
CGI-C number (%) improved at end-point	SWSD Study 305	--	66 (74%)	37 (36%)
p-values compared to placebo		--	<i>p</i> = 0.0001	not applicable

Percent of patients with at least minimal improvement at endpoint on CGI-C

Table 2: Summary of clinical trial data in patients with narcolepsy or OSAHS following treatment with modafinil

	Maintenance of Wakefulness Test		Epworth Sleepiness Scale	
	Modafinil 200 mg per day	Modafinil 400 mg per day	Modafinil 200 mg per day	Modafinil 400 mg per day
Disorder (Study)	Sleep latency difference (mins)^a	Sleep latency difference (mins)^a	ESS differenc e^a	ESS differenc e^a
	<i>p</i> value	<i>p</i> value	<i>p</i> value	<i>p</i> value

Narcolepsy (301) N=28 5	3.1	$p=0.00$ 01	3.8	$p=0.00$ 01	2.2	$p=0.0005$	2.9	$p=0.0001$
Narcolepsy (302) N=27 3	2.9	$p=0.00$ 01	2.6	$p=0.00$ 01	2.6	$p=0.0001$	4.0	$p=0.0001$
OSAHS (303) N=32 7	2.7	$p=0.00$ 01	2.6	$p=0.00$ 01	2.7	$p=0.0001$	2.7	$p=0.0001$

Data in changes from baseline to endpoint for modafinil vs placebo, unless otherwise stated

^a Positive value = modafinil better than placebo, negative value = modafinil worse than placebo

^b Difference in absolute value over placebo at endpoint

Table 3: SWSD study 305 sleep latency (mins) from MSLT at endpoint

		Modafinil 200mg (N=86)	Placebo (N=96)	p-value (ANOVA)
Baseline	<i>mean ± sd</i>	2.07 ± 1.53	2.04 ± 1.82	
Endpoint	<i>mean ± sd</i>	3.77 ± 4.32	2.37 ± 2.73	
Change at endpoint	<i>mean ± sd</i> <i>range</i>	1.70 ± 3.79 - 4.1 to 14.0	0.34 ± 2.77 -10.9 to 8.1	0.0022

INDICATIONS

MODAVIGIL[®] 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 or any other component of the product.
- Use in pregnancy.

PRECAUTIONS

Serious Skin Rash, including Stevens-Johnson Syndrome

Serious rash requiring hospitalization and discontinuation of treatment has been reported in adults and children in association with the use of modafinil.

Modafinil is not approved for use in pediatric 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 pediatric patients (age <17 years); these rashes included 1 case of possible Stevens-Johnson Syndrome (SJS) and 1 case of apparent multiorgan 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 pediatric 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 (see “**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.

While little is known about factors that can predict the risk of occurrence or the severity of rash associated with modafinil, the risk may increase with higher doses. Nearly all cases of serious rash associated with modafinil 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 modafinil, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, modafinil should ordinarily 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.

Multi-organ Hypersensitivity Reactions

Multi-organ hypersensitivity reactions have occurred in close temporal association to the initiation of modafinil. Although there have only 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 associated with modafinil. Signs and symptoms of these reactions 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, MODAVIGIL® should be discontinued and not restarted. 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.

Psychiatric Symptoms and Disorders

Psychiatric adverse experiences have been reported in patients treated with modafinil in clinical trials and from post-marketing experience. Patients should be monitored for the development of *de novo* psychiatric disorders or exacerbation of pre-existing psychiatric disorders at every adjustment of dose and regularly during treatment. If psychiatric symptoms develop in association with modafinil treatment, discontinuation of modafinil may be required. Caution should be exercised in giving

modafinil to patients with a history of psychiatric disorders including psychosis, depression, mania, major anxiety, agitation, insomnia or substance abuse.

Aggressive or hostile behaviour

The onset or worsening of aggressive or hostile behaviour has been reported in patients treated with modafinil. Patients treated with modafinil should be carefully monitored for the appearance or worsening of aggressive or hostile behaviour. If symptoms occur, modafinil should be discontinued.

Suicidal ideation and suicide-related behaviour

Suicidal ideation and suicide-related behaviour (including suicide attempts) have been reported in patients treated with modafinil. Patients treated with modafinil should be carefully monitored for the appearance or worsening of suicidal thinking and/or suicide-related behaviour. If suicide-related symptoms develop in association with modafinil, treatment should be discontinued.

Psychotic or manic symptoms

The onset or worsening of psychotic symptoms or manic symptoms (including hallucinations, delusions, agitation or mania) has been reported in patients treated with modafinil. Patients treated with modafinil should be carefully monitored for the appearance or worsening of psychotic or manic symptoms. If psychotic or manic symptoms occur, modafinil should be discontinued.

Bipolar disorders

Care should be taken in using modafinil in patients with co-morbid bipolar disorder because of concern for possible precipitation of a mixed/manic episode in such patients.

Depression

The onset of depression or the aggravation of underlying depressive disorder has been reported in patients treated with modafinil. Patients treated with modafinil should be carefully monitored for the appearance of or worsening of depression.

Anxiety

The onset or worsening of anxiety has been reported in patients treated. Anxiety and nervousness are adverse events that appear to be closely dose related.

General

Although modafinil has not been shown to produce functional impairment, any drug affecting the CNS may alter judgment, thinking or motor skills. Patients with major anxiety should only receive treatment with MODAVIGIL[®] in a specialist unit.

If a hypersensitivity reaction is suspected, MODAVIGIL[®] treatment should be discontinued.

In patients with obstructive sleep apnoea/hypopnoea syndrome, the underlying condition and any associated cardiovascular pathology should be monitored.

Patients should be advised that MODAVIGIL[®] is not a replacement for sleep and good sleep hygiene should be maintained.

Effects on Ability to Drive and Use Machines

Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that MODAVIGIL[®] therapy will not adversely affect their ability to engage in such activities.

Cardiovascular System

In hypertensive patients, blood pressure should be adequately controlled before initiating treatment with modafinil and monitored regularly during treatment. Blood pressure, heart rate and general cardiovascular status should be monitored in all patients during treatment with MODAVIGIL[®].

In clinical studies of MODAVIGIL[®], signs and symptoms including chest pain, palpitations, dyspnoea and transient ischaemic T-wave changes on ECG were observed in three subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that MODAVIGIL[®] not be used in patients with a history of left ventricular hypertrophy or ischaemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use.

The safety of MODAVIGIL[®] has not been established in patients with coronary artery disease, a recent history of myocardial infarction or unstable angina. Patients with these conditions were not included in the controlled clinical trials. Post marketing adverse events of ischaemic heart disease have been reported in patients with and without a history of cardiovascular disease while being treated with MODAVIGIL[®]. The risks of using MODAVIGIL[®] in patients with coronary artery disease, a recent history of myocardial infarction or unstable angina should be carefully weighed against the potential therapeutic benefit. It is recommended that such patients receive further specialist evaluation before MODAVIGIL[®] treatment is considered.

Postmarketing adverse events of cardiac arrhythmia, such as atrial fibrillation and premature ventricular contractions, have been reported in patients treated with MODAVIGIL[®]. In some of these cases there was a close temporal association to the use of MODAVIGIL[®], a resolution of the arrhythmia upon drug discontinuation and, in a few cases, a recurrence of arrhythmia after MODAVIGIL[®] rechallenge. It is recommended that patients have an ECG before MODAVIGIL[®] is initiated. Patients with abnormal findings should receive further specialist evaluation before MODAVIGIL[®] treatment is considered.

Dose Dependency and adverse effects

The development of skin and hypersensitivity reactions, central nervous system, psychiatric and cardiovascular system adverse reactions appear to be related to higher doses of modafinil. Cardiovascular and central nervous system adverse reactions increase significantly after a total daily dose of more than 400 mg. Always start at the lowest recommended dose (see “**DOSAGE AND ADMINISTRATION**”).

Patients (Women) Using Contraception

Sexually active women of child-bearing potential should be established on a contraceptive program before taking MODAVIGIL[®]. The effectiveness of oral contraceptives may be impaired due to enzyme induction activity of MODAVIGIL[®]. Alternative or concomitant methods of contraception are recommended for patients treated with MODAVIGIL[®], and for one month after discontinuation of treatment (see “**Interaction with Other Drugs**”).

Carcinogenicity and Mutagenicity

Carcinogenicity studies were conducted in which modafinil was administered in the diet to mice for 78 weeks and to rats for 104 weeks at doses up to 60 mg/kg/day. The highest dose studied in these studies would have achieved systemic exposure levels less than human exposure at the maximum recommended dose. There was no evidence of tumourigenesis associated with modafinil administration in these studies; however, the carcinogenic potential of modafinil has not been fully evaluated.

There was no consistent evidence for genotoxic activity of modafinil in *in vitro* assays of gene mutation (reverse mutation in *S. typhimurium* and *E. coli*, forward mutation in Chinese hamster V79 fibroblasts) or in the chromosomal damage assay (human lymphocytes *in vitro*, Chinese hamster bone marrow cells *in vivo*, mouse micronucleus assay). Modafinil did not increase unscheduled DNA synthesis in rat hepatocytes. In a cell transformation assay in BALB/3T3 mouse embryo cells, modafinil did not cause an increase in the frequency of transformed foci in the presence or absence of metabolic activation.

Impairment of Fertility

No effects on fertility were observed in male or female rats treated with modafinil prior and throughout mating and gestation at oral doses up to 100 mg/kg/day (the highest dose investigated would have achieved systemic exposure levels less than human exposure at the maximum recommended dose). However, sufficiently high enough doses or large enough sample sizes to adequately assess effects on fertility were not used in the study.

Use in Pregnancy (Category B3)

Animal studies to assess the effects of modafinil on reproduction and the developing foetus were not conducted at adequately high doses or according to guidelines which would have been able to provide a comprehensive evaluation of the potential of modafinil to adversely affect fertility, or cause embryoletality or teratogenicity.

Embryotoxicity, in the absence of maternal toxicity, was observed in rats receiving oral modafinil throughout the period of organogenesis. At a dose of 200 mg/kg/day (less than human exposure at the maximum recommended daily clinical dose of 400 mg), there was an increase in resorption, hydronephrosis and skeletal variations. The no effect dose for these effects was 100 mg/kg/day. Embryotoxicity was not observed in rabbits receiving oral modafinil throughout organogenesis at doses up to 100 mg/kg/day (0.6 times the human exposure at the maximum recommended daily dose of 400 mg, based on AUC). However, neither of these studies used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the foetus has not been characterised. Modafinil was embryotoxic in rats dosed during late gestation and lactation, or prior to and throughout mating and gestation, at oral doses \geq 50 mg/kg/day; the no effect dose was 20 mg/kg/day (less than human exposure at the maximum recommended clinical daily dose of 400 mg).

As there are no adequate and well-controlled trials with MODAVIGIL[®] in pregnant women, it should be contraindicated during pregnancy.

Patients should be cautioned regarding the potential increased risk of pregnancy when using steroidal contraceptives with MODAVIGIL[®] and for one month after discontinuation of therapy (see “**Interaction with Other Drugs**”).

Use in Lactation

No developmental toxicity was noted postnatally in the offspring of rats given oral modafinil up to 100 mg/kg/day during late gestation and throughout lactation. The highest dose studied in these studies would have achieved systemic exposure levels less than human exposure at the maximum recommended dose.

Modafinil and/or its metabolites have been found in the milk of lactating rats. It is not known whether modafinil or its metabolites are excreted in human milk. Therefore, breastfeeding is not recommended during administration of modafinil.

Abuse and Dependence Potential

In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, MODAVIGIL[®] may produce psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings. In *in vitro* binding studies, modafinil binds with low affinity 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. Caution should be exercised in administering modafinil to patients with history of alcohol, drug or illicit substance abuse. Patients with such history should be monitored for signs of misuse or abuse (e.g. increasing the recommended dosage).

Withdrawal: In one US Phase 3 clinical trial of nine weeks of MODAVIGIL[®] use, the effects of modafinil cessation were monitored for 14 days. No specific symptoms of

withdrawal were observed during the 14 days; however, sleepiness returned in patients with narcolepsy.

Use in Children and Adolescents (<18 years of age)

The efficacy and safety of MODAVIGIL® in this age group has not been established. MODAVIGIL® is not approved for use in paediatric patients for any indication. The use of MODAVIGIL® in this age group is not recommended. Neuropsychiatric and serious skin reactions have been reported in children and adolescents treated with MODAVIGIL®.

Special Populations

Use in the Elderly: There are no satisfactory data on the safety and efficacy of MODAVIGIL® in patients ≥ 65 years of age. The clearance of modafinil may be reduced in the elderly (see “**DOSAGE AND ADMINISTRATION**”).

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 (an inactive metabolite) was increased 9-fold (see “**DOSAGE AND ADMINISTRATION**”).

Hepatic Impairment: The dose of MODAVIGIL® should be reduced by half in patients with severe hepatic impairment (see “**DOSAGE and ADMINISTRATION**”).

INTERACTIONS WITH OTHER MEDICINES

CNS Active Drugs

Methylphenidate – The absorption of MODAVIGIL® may be delayed by approximately one hour when co-administered with methylphenidate.

Clomipramine – The coadministration of a single dose of clomipramine (50 mg) on the first three days of treatment with modafinil (200 mg/day) in healthy volunteers did not show an effect on the pharmacokinetics of either drug. However, one incident of increased levels of clomipramine and its active metabolite desmethylclomipramine has been reported in a CYP2D6 poor metabolizer with narcolepsy during treatment with modafinil. (See “*Potential Interactions with Drugs That Inhibit or are Metabolised by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes*”).

Triazolam – In healthy, female volunteers, who were receiving long-term treatment with ethinyl estradiol, the co-administration of two single doses of 0.125 mg of triazolam (one administered before and the other at the end of treatment) with modafinil (200 mg for seven days, followed by 400 mg for 21 days) indicated that, for triazolam, the C_{max} and AUC_{0-∞} were reduced by 59% and 42% respectively, and the elimination rate was increased by approximately 50%. Therefore, dosage adjustment of triazolam may be necessary when co-administered with MODAVIGIL®.

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

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

Diazepam, Phenytoin, Propranolol, Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors – Because modafinil is a reversible inhibitor of the drug-metabolising enzyme CYP2C19, co-administration of MODAVIGIL[®] with drugs such as diazepam, phenytoin, and propranolol, which are largely eliminated via that pathway, may increase the circulating levels of those compounds. In addition, in individuals deficient in the enzyme CYP2D6, the levels of CYP2D6 substrates such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which have ancillary routes of elimination through CYP2C19, may be increased by co-administration of modafinil. Dose adjustments may be necessary for patients being treated with these and similar medications.

Steroidal Contraceptives, Cyclosporin, Theophylline – Chronic administration of MODAVIGIL[®] also causes modest induction of the metabolising enzyme CYP3A4, thus reducing the levels of co-administered substrates for that enzyme system, such as steroidal contraceptives, cyclosporin and to a lesser degree, theophylline. Dose adjustments may be necessary for patients being treated with these and similar medications.

Inducers or Inhibitors of CYP3A4 – Co-administration of potent inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampicin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) could alter the levels of modafinil due to the partial involvement of that enzyme in the metabolic elimination of the compound (see “**Patients (Women) Using Contraception**”).

Warfarin, Phenytoin – The exposure of human hepatocytes to modafinil *in vitro* produced an apparent concentration-related suppression of expression of CYP2C9 activity. The clinical relevance of this finding is unclear, since no other indication of CYP2C9 suppression has been observed. However, monitoring of prothrombin times is suggested as a precaution for the first several months of co-administration of MODAVIGIL[®] and warfarin, a CYP2C9 substrate, and thereafter whenever MODAVIGIL[®] dosing is changed. In addition, patients receiving MODAVIGIL[®] and phenytoin, a CYP2C9 substrate, concomitantly should be monitored for signs of phenytoin toxicity.

It should be noted that evaluation of drug interactions based on *in vitro* systems might not necessarily reflect those seen *in vivo* situations. This information should be used as a guide to assess the risks associated with the use of concomitant medications.

ADVERSE EFFECTS

Modafinil has been evaluated for safety in over 3500 patients, of whom more than 2000 patients with excessive sleepiness associated with primary disorders of sleep and wakefulness were given at least one dose of modafinil. In clinical trials, modafinil has been found to be generally well tolerated and most adverse experiences were mild to moderate.

The most commonly observed adverse events ($\geq 5\%$) associated with the use of MODAVIGIL[®] more frequently than placebo-treated patients in the placebo-controlled clinical studies in primary disorders of sleep and wakefulness were headache, nausea, nervousness, rhinitis, diarrhoea, back pain, anxiety, insomnia,

dizziness, and dyspepsia. The adverse event profile was similar across these studies.

In the placebo-controlled clinical trials, 74 of the 934 patients (8%) who received MODAVIGIL[®] discontinued due to an adverse experience compared to 3% of patients that received placebo. The most frequent reasons for discontinuation that occurred at a higher rate for MODAVIGIL[®] than placebo patients were headache (2%), nausea, anxiety, dizziness, insomnia, chest pain and nervousness (each <1%). In a Canadian clinical trial, a 35 year old obese narcoleptic male with a prior history of syncopal episodes experienced a 9-second episode of asystole after 27 days of modafinil treatment (300 mg/day in divided doses).

Incidence in Controlled Trials

The following table (Table 4) presents the adverse experiences that occurred at a rate of 1% or more and were more frequent in patients treated with MODAVIGIL[®] than in placebo patients in the principal, placebo-controlled clinical trials.

The prescriber should be aware that the figures provided below cannot be used to predict the frequency of adverse experiences in the course of usual medical practice, where patient characteristics and other factors may differ from those occurring during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. Review of these frequencies, however, provides prescribers with a basis to estimate the relative contribution of drug and non-drug factors to the incidence of adverse events in the population studied.

Table 4. Incidence of Treatment-Emergent Adverse Experiences in Parallel-Group, Placebo-Controlled Clinical Trials¹ in Narcolepsy, OSAHS, and SWSD with MODAVIGIL® (200mg. 300mg. 400mg).

Body System	Preferred Term	Modafinil (n=934, %)	Placebo (n=567, %)
Body as a whole	Headache	34	23
	Back pain	6	5
	Flu syndrome	4	3
	Chest pain	3	1
	Chills	1	0
	Neck rigidity	1	0
	Cardiovascular system	Hypertension	3
Tachycardia		2	1
Palpitation		2	1
Vasodilatation		2	0
Digestive system	Nausea	11	3
	Diarrhoea	6	5
	Dyspepsia	5	4
	Dry mouth	4	2
	Anorexia	4	1
	Constipation	2	1
	Abnormal liver function ²	2	1
	Flatulence	1	0
	Mouth ulceration	1	0
	Thirst	1	0
	Haemic/Lymphatic system	Eosinophilia	1
Metabolic/Nutritional	Oedema	1	0
Nervous	Nervousness	7	3
	Insomnia	5	1
	Anxiety	5	1
	Dizziness	5	4
	Depression	2	1
	Paraesthesia	2	0
	Somnolence	2	1
	Hypertonia	1	0
	Dyskinesia ³	1	0
	Hyperkinesia	1	0
	Agitation	1	0
	Confusion	1	0
	Tremor	1	0
	Emotional lability	1	0
	Vertigo	1	0
Respiratory	Rhinitis	7	6
	Pharyngitis	4	2
	Lung disorder	2	1
	Epistaxis	1	0
	Asthma	1	0

Skin/Appendages	Sweating	1	0
	Herpes simplex	1	0
Special Senses	Amblyopia	1	0
	Abnormal vision	1	0
	Taste perversion	1	0
	Eye pain	1	0
Urogenital	Urine abnormality	1	0
	Haematuria	1	0
	Pyuria	1	0

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

1. Events reported by at least 1% of patients treated with MODAVIGIL[®] that were more frequent than in the placebo group are included; incidence is rounded to the nearest 1%. The adverse experience terminology is coded using a standard modified COSTART Dictionary.

Events for which the MODAVIGIL[®] incidence was at least 1%, but equal to or less than placebo are not listed in the table. These events included the following: infection, pain, accidental injury, abdominal pain, hypothermia, allergic reaction, asthenia, fever, viral infection, neck pain, migraine, abnormal electrocardiogram, hypotension, tooth disorder, vomiting, periodontal abscess, increased appetite, ecchymosis, hyperglycaemia, peripheral oedema, weight loss, weight gain, myalgia, leg cramps, arthritis, cataplexy, thinking abnormally, sleep disorder, increased cough, sinusitis, dyspepsia, bronchitis, rash, conjunctivitis, ear pain, dysmenorrhoea⁴, urinary tract infection

2. Elevated liver enzymes
3. Oro-facial dyskinesias
4. Incidence adjusted for gender

Post Marketing Experience

Post Marketing Experience for MODAVIGIL[®], 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

Rare Palpitations
 Very rare Ischaemic heart disease, cardiac arrhythmias

Gastrointestinal disorders

Rare Dry mouth, nausea, diarrhoea, vomiting, abdominal pain

General disorders

Rare Tolerance, chest pain, lack of efficacy, condition aggravated, malaise, fatigue

Very rare Oedema

Immune system disorders

Very rare Multi-organ system hypersensitivity reactions, urticaria (hives),
angioedema, anaphylaxis

Investigations

Rare Increased hepatic enzymes, increased gamma-GT, weight increase,
weight decrease, blood pressure increased

Very Rare Abnormal ECG

Musculoskeletal and connective tissue disorders

Rare Muscle weakness

Nervous system disorders

Uncommon Headache

Rare Dizziness, tremor, paraesthesia, dyskinesia

Very rare Dyskinesias, including reports of tardive dyskinesia; convulsions

Psychiatric disorders

Rare Nervousness, agitation, irritability, psychomotor hyperactivity,
depression, anxiety, confusion, insomnia, suicide attempt, aggravated
depression, psychosis, mania, delusions, hallucinations, suicidal
ideation, thinking abnormal and aggression

Renal and urinary disorders

Rare Foul urine odour

Skin and subcutaneous tissue disorders

Rare Rash, acne, eczema, pruritus

Very rare Serious or life threatening rash, including erythema multiforme, Stevens
Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug
Rash with Eosinophilia and System Symptoms (DRESS), and
hyperhidrosis

Vascular disorders

Rare Hypertension

DOSAGE AND ADMINISTRATION

MODAVIGIL® should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of either narcolepsy, OSAHS, and/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 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) (see “**CLINICAL TRIALS**”).

Treatment with MODAVIGIL® 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 dose of MODAVIGIL® is 200 to 400 mg/day, given as a single dose in the morning, or as two divided doses, in the morning and at noon. Tablets should be swallowed whole.

Doses of 400 mg/day have been well tolerated, but there is no statistically significant evidence that this dose confers additional benefit beyond that of the 200 mg dose.

For patients who require more than 200 mg/day, the dose should be increased, to a maximum of 400 mg/day, in increments of 100 mg as needed and tolerated.

Obstructive Sleep Apnoea/Hypopnoea Syndrome

In OSAHS, MODAVIGIL® is indicated as an adjunct to continuous positive airway pressure (CPAP). A maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating MODAVIGIL®. If MODAVIGIL® is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

The dose of MODAVIGIL® is 200 to 400 mg/day, given as a single dose in the morning, or as two divided doses, in the morning and at noon. Tablets should be swallowed whole.

Doses of 400 mg/day have been well tolerated, but there is no statistically significant evidence that this dose confers additional benefit beyond that of the 200 mg dose.

For patients who require more than 200 mg/day, the dose should be increased, to a maximum of 400 mg/day, in increments of 100 mg as needed and tolerated.

Moderate to Severe Chronic Shift Work Sleep Disorder

The recommended daily dose is 200mg. MODAVIGIL® should be taken as a single dose approximately 1 hour prior to the start of the work shift. Tablets should be swallowed whole.

Dosing in Special Populations

In patients with severe hepatic impairment, the dose of MODAVIGIL® should be reduced to one-half of that recommended for patients with normal hepatic function (see “**PRECAUTIONS**”).

There is inadequate information to determine safety and efficacy of MODAVIGIL® dosing in patients with severe renal impairment (see “**PRECAUTIONS**”).

In elderly patients, elimination of MODAVIGIL® 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 “**PRECAUTIONS**”).

OVERDOSAGE

Symptoms

A small number of individuals have each taken MODAVIGIL® at doses of 1000 mg/day (2.5 times the maximum recommended daily dose of 400 mg) or more. The adverse experiences observed were limited, expected and non-life threatening, and the patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia and slight or moderate elevations in haemodynamic parameters. No specific organ toxicities were observed. Other observed high dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhoea and decreased prothrombin time.

Death has occurred with modafinil overdose alone or in combination with other drugs. Symptoms 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 diarrhea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain.

Management

Management of overdose is primarily symptomatic, as no specific antidote to the toxic effects of modafinil overdose has been identified. Overdoses should be managed empirically, with supportive care, including cardiovascular monitoring.

Contact the Poisons Information Centre on 131 126 for further advice on overdose management

PRESENTATION AND STORAGE CONDITIONS

MODAVIGIL® is a tablet containing 100 mg of modafinil, debossed with “100” on one side.

It is registered in packs of 10, 30, 60 and 90* tablets supplied in PVC/PVDC/Al blister strips, each of which contains 10 tablets.

Store below 25 degrees C, protect from light and moisture.

NAME AND ADDRESS OF SPONSOR

In Australia:
Teva Pharma Australia Pty Ltd
Level 2, 37 Epping Rd
Macquarie Park NSW 2113

In New Zealand:
bioCSL (NZ) Ltd.
Auckland
New Zealand

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST ENTRY ON TO THE ARTG

26 March 2007

Date of most recent amendment: 14 Sept 2015

*not marketed