PACKAGE INSERT – PROVIGIL® 100 (Tablets)

SCHEDULING STATUS S5

PROPRIETARY NAME (and dosage form)

PROVIGIL 100 (Tablets)

COMPOSITION

Each tablet contains 100 mg modafinil.

PHARMACOLOGICAL CLASSIFICATION

A 1.1 Central analeptics

PHARMACOLOGICAL ACTION

Pharmacodynamics

The mechanism(s) through which modafinil promotes wakefulness is unknown. Modafinil has wake-promoting actions like sympathomimetic agents including amphetamine and methylphenidate, although the pharmacological profile is not identical to that of sympathomimetic amines.

At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil also does not inhibit the activities of MAO-B or phosphodiesterases II-V.

Modafinil is not a direct- or indirect-acting dopamine receptor agonist and is inactive in several *in vivo* pre-clinical models capable of detecting enhanced dopaminergic activity. *In vitro*, modafinil binds to the dopamine reuptake site and causes an increase in extra-cellular dopamine, but no increase in dopamine release. In a pre-clinical model the wakefulness induced by amphetamine, but not modafinil, is antagonised by the dopamine receptor

antagonist haloperidol.

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

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

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

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

Pharmacokinetics

Modafinil is a racemic compound whose enantiomers have different pharmacokinetics (e.g., the half-life of the *l*-isomer is approximately three times that of the *d*-isomer in humans). The enantiomers do not interconvert. At steady state, total exposure to the *l*-isomer is

approximately three times that for 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. The effective elimination half-life of modafinil after multiple doses is about 15 hours. The enantiomers of modafinil exhibit linear kinetics upon multiple dosing of 200 to 600 mg/day once daily in healthy volunteers. Apparent steady states of total modafinil and *l*-(-)-modafinil are reached after 2 to 4 days of dosing.

Absorption and Distribution

Absorption of PROVIGIL tablets is rapid, with peak plasma concentrations occurring at 2 to 4 hours. The bioavailability of PROVIGIL tablets is approximately equal to that of an aqueous suspension. The absolute oral bioavailability was not determined due to the aqueous insolubility (<1 mg/ml) of modafinil, which precluded intravenous administration. Food has no effect on overall PROVIGIL bioavailability; 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). In human plasma, *in vitro*, modafinil is moderately bound to plasma protein (~60 %, 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. Even at much larger concentrations (1000 μM; >25 times the C_{max} of 40 μM at steady state at 400 mg/day), modafinil has no effect on warfarin binding. Modafinil acid at concentrations >500 μM decreases the extent of warfarin binding, but these concentrations are >35 times those achieved therapeutically.

Metabolism and Elimination

The major route of elimination (~90 %) is metabolism, primarily by the liver, with subsequent renal elimination of the metabolites. Urine alkalinisation has no effect on the elimination of modafinil.

Metabolism occurs through hydrolytic deamidation, 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 radio-labelled modafinil 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). The largest fraction of the drug in urine was modafinil acid, but at least six other metabolites were present in lower concentrations. Only two metabolites reach appreciable concentrations in plasma, i.e. modafinil acid and modafinil sulfone. In pre-clinical 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 ≥400 mg/day. Induction of hepatic metabolising enzymes, most importantly cytochrome P-450 (CYP) 3A4, has also been observed *in vitro* after incubation of primary cultures of human hepatocytes with modafinil. (For further discussion of the effects of modafinil on CYP enzyme activities (see INTERACTIONS).

Interactions: Because modafinil is a reversible inhibitor of the enzyme CYP2C19, co-administration of modafinil with medicines such as diazepam, phenytoin and propranolol, which are largely eliminated via that pathway, may increase the circulating levels of those compounds. In addition, in individuals deficient in the enzyme CYP2D6 (i.e. 7 to 10 % of the caucasian population; similar or lower in other populations), the levels of CYP2D6 substrates such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which have ancillary routes of elimination through CYP2C19 may be increased by co-administration of modafinil. Dose adjustments may be necessary for patients being treated with these and similar medications (see INTERACTIONS).

Chronic administration of modafinil may also cause 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 (see INTERACTIONS).

An apparent concentration-related suppression of CYP2C9 activity was observed in human

hepatocytes after exposure to modafinil *in vitro*. Although no other indication of CYP2C9 suppression has been observed, the *in vitro* results suggest that there is potential for metabolic interaction between PROVIGIL and CYP2C9 substrates, such as warfarin or phenytoin (see INTERACTIONS).

Special Populations

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

Age Effect: A slight decrease (~20 %) in the oral clearance (CL/F) of modafinil was observed in a single dose study at 200 mg in 12 subjects with a mean age of 63 years (range 53 to 72 years), but the change was considered unlikely to be clinically significant. In a multiple dose study (300 mg/day) in 12 patients with a mean age of 82 years (range 67 to 87 years), the mean levels of modafinil in plasma were approximately two times those historically obtained in matched younger subjects. Due to potential effects from the multiple concomitant medications with which most of the patients were being treated, the apparent difference in modafinil pharmacokinetics may not be attributable solely to the effects of aging. However, the results suggest that the clearance of modafinil may be reduced in the elderly (see DOSAGE AND DIRECTIONS FOR USE).

Race Effect: The influence of race on the pharmacokinetics of modafinil 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 (an inactive metabolite) was increased 9 fold (see WARNINGS, Precautions).

Hepatic Impairment: Pharmacokinetics and metabolism were examined in patients with cirrhosis of the liver (6 M and 3 F). Three patients had stage B or B+ cirrhosis (per the Child Pugh criteria) and 6 patients had stage C or C+ cirrhosis. Clinically 8 of 9 patients were icteric and all had ascites. In these patients, the oral clearance of modafinil was decreased by about 60% and the steady state concentration was doubled compared to normal patients.

The dose of PROVIGIL should be reduced in patients with severe hepatic impairment (see WARNINGS, Precautions and DOSAGE AND DIRECTIONS FOR USE.)

INDICATIONS

PROVIGIL is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, as defined by either of the two following DSM IV criteria in the absence of other clinically significant medical or psychotic conditions:

1) 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

2) a Complaint of excessive sleepiness or sudden muscle weakness with associated features: sleep paralysis, hypnagogic hallucinations, automatic behaviours, disrupted major sleep episodes; and polysomnography demonstrating one of the following: sleep latency less than 10 minutes or rapid eye movement (REM) sleep latency less than 20 minutes.

The effectiveness of PROVIGIL has not been evaluated in placebo-controlled studies of more than 9 weeks.

CONTRA-INDICATIONS

- Patients with a known hypersensitivity to PROVIGIL.
- Major anxiety (outside specialised units).
- Children and adolescents under the age of 16 years.
- Severe renal impairment.

WARNINGS

Periodic specialist clinical assessment is necessary. Patients with major anxiety should only receive treatment with PROVIGIL in a specialist unit.

Blood pressure and heart rate should be monitored in hypertensive patients. It is recommended that PROVIGIL 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 central nervous system stimulant use.

Precautions

General

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

Cardiovascular System

In clinical studies of PROVIGIL, 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 PROVIGIL tablets 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.

PROVIGIL 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.

PROVIGIL has not been systematically evaluated in patients with hypertension. Periodic monitoring of hypertensive patients may be appropriate.

Central Nervous System

One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of PROVIGIL and sleep deprivation. There was no evidence of psychosis 36 hours after drug discontinuation.

Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.

Patients with Severe Renal Impairment

In patients with severe renal impairment (mean creatinine clearance = 16,6 ml/min), a 200 mg single dose of PROVIGIL did not lead to increased exposure to modafinil but resulted in much higher exposure to the inactive metabolite, modafinil acid, than is seen in subjects with normal renal function. There is little information available about the safety of such levels of this metabolite (see PHARMACOLOGICAL ACTION).

Patients with Severe Hepatic Impairment

In patients with severe hepatic impairment, with or without cirrhosis (see PHARMACOLOGICAL ACTION) PROVIGIL should be administered at a reduced dose as the clearance of modafinil was decreased compared to that in normal subjects (see DOSAGE AND DIRECTIONS FOR USE).

Elderly Patients

To the extent that elderly patients may have diminished renal and/or hepatic function, dosage reductions should be considered (see DOSAGE AND DIRECTIONS FOR USE).

Patients Using Contraceptives

The effectiveness of hormonal contraceptives may be reduced when used with PROVIGIL tablets and for one month after discontinuation of therapy (see INTERACTIONS *Potential Interactions with Drugs That Inhibit, Induce, or are Metabolised by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes*). Alternative or concomitant methods of contraception are recommended for patients treated with PROVIGIL tablets, and for one month after discontinuation of PROVIGIL.

Information for Patient

Doctors are advised to discuss the following issues with patients for whom they prescribe PROVIGIL tablets.

Lactation

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

Concomitant Medication

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

Alcohol

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

Allergic Reactions

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

INTERACTIONS

Oral Contraceptives

The effectiveness of oral contraceptives may be impaired due to enzyme induction activity of PROVIGIL. When oral contraceptives are used, a product containing 50 micrograms or more of ethinyl oestradiol should be taken. Adequate contraception will require continuation of the oral contraceptive for two cycles after stopping PROVIGIL.

Tricyclic Antidepressants

Patients receiving tricyclic antidepressants e.g. clomipramine, should be carefully monitored.

Anticonvulsant Therapy

Care should be observed with co-administration of anticonvulsant therapy in view of the enzyme inducing potential of PROVIGIL.

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

Chronic dosing of PROVIGIL at 400 mg/day once daily resulted in a ~20% mean decrease in modafinil plasma trough concentrations by week 9, relative to those at week 3, suggesting that chronic administration of PROVIGIL might have caused induction of its metabolism.

In addition, co-administration of potent inducers of CYP3A4 (e.g. carbamazepine, phenobarbital, rifampin) 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.

In *in vitro* studies using primary human hepatocyte cultures, PROVIGIL was shown to slightly induce CYP1A2, CYP2B6 and CYP3A4 in a concentration-dependent manner. Although induction results based on *in vitro* experiments are not necessarily predictive of response *in vivo*, caution needs to be exercised when PROVIGIL is co-administered with drugs that depend on these three enzymes for their clearance. Specifically, lower blood levels of such drugs could result. In the case of CYP1A2 and CYP2B6, no other evidence of enzyme induction has been observed. A modest induction of CYP3A4 by PROVIGIL has been indicated by other results, hence the clearance of CYP3A4 substrates such as cyclosporine, hormonal contraceptives and, to a lesser degree, theophylline, may be increased.

The exposure of human hepatocytes to PROVIGIL *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 PROVIGIL and warfarin, a CYP2C9 substrate, and thereafter whenever PROVIGIL dosing is changed. In addition, patients receiving PROVIGIL and phenytoin, a CYP2C9 substrate, concomitantly should be monitored for signs of phenytoin toxicity.

In vitro studies using human liver microsomes showed that PROVIGIL has little or no capacity to inhibit the major CYP enzymes except for CYP2C19, which is reversibly inhibited at pharmacologically relevant concentrations of modafinil. Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, phenytoin or S-mephenytoin may have prolonged elimination upon co-administration with PROVIGIL and may require dosage reduction.

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

Other

Interaction studies with monoamine oxidase inhibitors, central nervous system-active drugs and cardiovascular drugs have not been performed and caution is advised when concomitantly administering these drugs and PROVIGIL. Concomitant administration of PROVIGIL and methylphenidate did not result in clinically important alterations in the pharmacokinetic profiles of both medicines.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

Animal studies to assess the effects of PROVIGIL on reproduction and the developing foetus were not conducted at adequately high doses or according to guidelines which would ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect fertility, or cause embryo lethality or teratogenicity.

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

DOSAGE AND DIRECTIONS FOR USE

Adults

The dose of PROVIGIL is 200 mg/day, given as a single dose in the morning.

Doses of 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose.

Elderly

In elderly patients, elimination of PROVIGIL 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.

Hepatic failure

The dose in patients with hepatic failure should be reduced by half (100-200 mg/day).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-Effects

The most adverse experiences with PROVIGIL were mild to moderate.

The most common observed adverse events (≥ 5 %) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, anxiety and insomnia.

Refer to the following tabulated summary of adverse experiences that occurred in narcolepsy patients at a rate of 1 % or more and were more frequent in patients treated with PROVIGIL than in placebo patients in US placebo-controlled clinical studies.

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 medicine practice, where patient characteristics and other factors may differ from those occurring during clinical studies.

Body System	Preferred Term[1]	Provigil (n = 369)	Placebo (n = 185)
Body as a Whole	Headache	50 %	40 %
	Chest Pain	2 %	1 %
	Neck Pain	2 %	1 %
	Chills	2 %	0 %
	Rigid Neck	1 %	0 %
	Fever/Chills	1 %	0 %
Digestive	Nausea	13 %	4 %
	Diarrhoea	8 %	4 %
	Dry mouth	5 %	1 %
	Anorexia	5 %	1 %
	Abnormal liver function[2]	3 %	2 %
	Vomiting	2 %	1 %
	Mouth ulcer	1 %	0 %
	Gingivitis	1 %	0 %
	Thirst	1 %	0 %
Respiratory System	Rhinitis	11 %	8 %
	Pharyngitis	6 %	3 %
	Lung disorders	4 %	2 %
	Dyspnoea	2 %	1 %
	Asthma	1 %	0 %
	Epistaxis	1 %	0 %
Nervous System	Nervousness	8 %	6 %
	Dizziness	5 %	4 %
	Depression	4 %	3 %
	Anxiety	4 %	1 %

	Cataplexy	3 %	2 %
	Insomnia	3 %	1 %
	Paraesthesia	3 %	1 %
	Dyskinesia[3]	2 %	0 %
	Hypertonia	2 %	0 %
	Confusion	1 %	0 %
	Amnesia	1 %	0 %
	Emotional lability	1 %	0 %
	Ataxia	1 %	0 %
	Tremor	1 %	0 %
Cardiovascular	Hypotension	2%	1%
	Hypertension	2%	0%
	Vasodilation	1%	0%
	Arrhythmia	1%	0%
	Syncope	1%	0%
Haemic/Lymphatic	Eosinophilia	2%	0%
Special Senses	Amblyopia	2%	1%
	Abnormal vision	2%	0%
Metabolic/Nutritional	Hyperglycaemia	1%	0%
	Albuminuria	1%	0%
Musculo-skeletal	Joint disorders	1%	0%
Skin/Appendages	Herpes simplex	1%	0%
	Dry skin	1%	0%
Urogenital	Abnormal urine	1%	0%
	Urinary retention	1%	0%
	Abnormal ejaculation[4]	1%	0%

[1] Events reported by at least 1 % of patients treated with PROVIGIL 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 PROVIGIL incidence was at least 1 %, but equal to or less than placebo are not listed in the table. These events included the following: Infection, back pain, hypothermia, abdominal pain, flu syndrome, allergic reaction, fever, asthaenia, accidental injury, general oedema, tachycardia, palpitations, migraine, ventricular extrasystole, bradycardia, dyspepsia, tooth disorders, constipation, flatulence, increased appetite, gastroenteritis, GI disorders, ecchymosis, anaemia, leukocytosis, peripheral oedema, increased weight, increased AST, myalgia, arthritis, arthralgia, somnolence, thinking abnormally, leg cramps, sleep disorder, hallucinations, hyperkinesia, decreased libido, increased cough, sinusitis, bronchitis, pneumonia, rash, sweating, pruritus, skin disorders, psoriasis, ear pain, eye pain, ear disorders, taste perversion, dysmenorrhoea[4], urinary tract infections, pyuria, haematuria, cystitis, and disturbed menses[4].

[2] Elevated liver enzymes.

[3] Oro-facial dyskinesias.

[4] Incidence adjusted for gender.

Additional side effects that have been reported are excitation, aggressive tendencies, personality disorders, central nervous system stimulation, euphoria and tremor.

The following side effects have been identified during post-approval use of PROVIGIL, but the frequency is unknown:

Central nervous system: Symptoms of psychosis, symptoms of mania.

Skin and Appendages: Serious skin reactions (including suspected cases of both erythema multiforme and Stevens-Johnson syndrome).

Body as a whole: Hypersensitivity: urticaria (hives), angioedema.

PROVIGIL may cause a positive reaction in tests used for the detection of drug abuse.

Drug Abuse and Dependence

Abuse Potential and Dependence

In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL 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. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies, PROVIGIL was also partially discriminated as stimulant-like. Doctors 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 PROVIGIL (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 PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate).

Withdrawal

The effects of PROVIGIL withdrawal were monitored following 9 weeks of PROVIGIL use in one US Phase 3 controlled clinical trial. No specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See “SIDE-EFFECTS”. Treatment is symptomatic and supportive.

Main symptom following massive ingestion is insomnia.

Management: Induced emesis or gastric lavage should be considered. Hospitalisation and surveillance of psychomotor status, cardiovascular monitoring or surveillance until the patient's symptoms have resolved.

IDENTIFICATION

A capsule-shaped white to off-white tablet debossed with '100' on one side.

PRESENTATION

30 tablets are packed into white opaque PVC/PVDC/aluminium blisters.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

37/1.1/0025

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