PRODUCT MONOGRAPH

Pr ALERTEC®*

modafinil tablets <Mfr. Std.>

100mg

Central Nervous System Stimulant

Teva Canada Limited
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Toronto, Ontario
Canada M1B 2K9

Marketed by:
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Control # 178544

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ALERTEC ®
(modafinil)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet 100mg	Lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, sodium croscarmellose

INDICATIONS AND CLINICAL USE

ALERTEC (modafinil) is indicated for the symptomatic treatment of excessive sleepiness in adult patients with narcolepsy, obstructive sleep apnea (OSA) and circadian rhythm sleep disorder, shift work type (shift work disorder) (SWD).

In OSA, ALERTEC is indicated as an adjunct to successful standard treatment(s) for the underlying obstruction, when excessive sleepiness persists. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient with OSA, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating ALERTEC. If ALERTEC is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

ALERTEC (modafinil) is indicated for the symptomatic treatment of excessive sleepiness (as confirmed by multiple sleep latency test) in SWD associated with loss of a normal sleep-wake pattern (as confirmed by polysomnography).

Daytime sleep (as measured by polysomnography) in SWD is not affected by the use of ALERTEC.

The effect of ALERTEC on night-shift work performance, sleep deficit in SWD, or performance following a night-shift have not been adequately evaluated in controlled studies.

The effectiveness of modafinil in long-term use (greater than 9 weeks in the narcolepsy clinical trials and 12 weeks in the OSA and SWD clinical trials) has not been systematically evaluated in placebo-controlled trials. The physician who elects to prescribe ALERTEC for an extended time in patients with narcolepsy, OSA or SWD should periodically re-evaluate long-term usefulness for the individual patient.

In narcolepsy, ALERTEC has no significant effect on cataplexy.

ALERTEC should not be used for the treatment of normal fatigue states. The safety and efficacy of ALERTEC has not been studied in this patient population (see **Warnings and Precautions**).

There is no evidence that normal levels of alertness can be heightened by ALERTEC.

Geriatrics:
Dyskinesias have been reported in the elderly with the use of ALERTEC. Elimination of modafinil and its metabolites may be reduced as a consequence of aging, and elderly patients have been found to be more sensitive to the effects of ALERTEC; these patients should be started at a lower dose. Caution should also be exercised when co-administration of modafinil and clomipramine is deemed necessary (see **Drug Interactions; Dosage and Administration; Action and Clinical Pharmacology**).

Pediatrics (<18 years of age):
Safety and effectiveness in pediatric patients have not been established. Serious skin rashes, including erythema multiforme major (EMM) and Stevens-Johnson Syndrome (SJS) have been associated with modafinil use in pediatric patients (see **Warnings and Precautions, Serious Rash, Including Stevens-Johnson Syndrome**).

ALERTEC is not approved for use in pediatric patients for any indication including Attention Deficit Hyperactivity Disorder.

CONTRAINDICATIONS

- Patients who are hypersensitive to modafinil, armodafinil (the R-enantiomer of modafinil; not marketed in Canada) or to any ingredient in the formulation or component of the container.
- ALERTEC is contraindicated in patients in agitated states and in patients with severe anxiety.

WARNINGS AND PRECAUTIONS

Serious 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 multi-organ hypersensitivity reaction. Several of the cases were associated with fever and other abnormalities (e.g., vomiting, leucopenia). 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. The reporting rate of TEN and SJS associated with modafinil use, which is generally accepted to be an underestimate due to under-reporting, 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.

There are no factors that are known to predict the risk of occurrence or the severity of rash associated with modafinil. 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.

Angioedema and Anaphylactoid Reactions

One serious case of angioedema and one case of hypersensitivity (with rash, dysphagia, and bronchospasm), were observed among 1,595 patients treated in clinical trials with armodafinil (not marketed in Canada), the R-enantiomer of modafinil (which is the racemic mixture). No such cases were observed in modafinil clinical trials.

Angioedema and anaphylactic reaction have been reported in post-marketing experience with modafinil.

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 days) to the initiation of modafinil.

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 associated with modafinil. 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, hematological 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, ALERTEC 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 ALERTEC should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking ALERTEC, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity.

Psychiatric Symptoms

Psychiatric adverse experiences have been reported in patients treated with ALERTEC. There have been reports of psychotic episodes associated with ALERTEC use. Post-marketing adverse events associated with the use of modafinil have included mania, delusions, hallucinations, and suicidal ideation and aggression, some resulting in hospitalization. Many, but not all, patients had a prior psychiatric history.

In the adult modafinil controlled trials database, psychiatric symptoms resulting in treatment discontinuation (at a frequency >0.3%) and reported more often in patients treated with modafinil compared to those treated with placebo were anxiety (1%), nervousness (1%), insomnia (<1%), confusion (<1%), agitation (<1%) and depression (<1%). Caution should be exercised when ALERTEC is given to patients with a history of psychosis, depression, or mania. Consideration should be given to the possible emergence or exacerbation of psychiatric symptoms in patients treated with ALERTEC. If psychiatric symptoms develop in association with ALERTEC administration, consider discontinuing ALERTEC.

In controlled clinical trials of pediatric patients with ADHD, adverse events categorized as signs and symptoms of psychosis or mania and/or suicidal ideation were reported in <1% of patients treated with modafinil and no patients treated with placebo. Aggression and violent behavior were reported in 1% of modafinil-treated patients and no placebo-treated patients in controlled clinical trials of pediatric patients with narcolepsy or OSA. There were no reports of psychosis or mania and/or suicidal ideation in clinical trials with this pediatric population.

Normal Fatigue States

ALERTEC should not be used for the treatment of normal fatigue states. One preliminary study in sleep-deprived subjects, employing a between-subject design (n=42) and a single dose (300mg), suggests that ALERTEC causes an increased self-estimate of performance which is not commensurate with actual changes in performance (i.e., overconfidence). A subsequent study in sleep-deprived subjects, employing a within-subject design (n=6), using 100mg administered three times over a period of 24 hours failed to demonstrate an adverse effect on the ability to judge one's own cognitive capabilities.

Occupational Hazards

There is evidence that, because of possible over-stimulation and overconfidence, ALERTEC alters the ability to perform hazardous activities in some patients. Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that ALERTEC therapy will not adversely affect their ability to engage in such activities.

CPAP Use in Patients with OSA

In OSA, ALERTEC is indicated as an adjunct to successful standard treatment(s) 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 ALERTEC. If ALERTEC is used adjunctively with CPAP, the encouragement of, and periodic assessment of, CPAP compliance is necessary.

Cardiovascular

Blood pressure and heart rate should be regularly monitored in patients receiving ALERTEC. ALERTEC should be discontinued in patients who develop arrhythmia or moderate to severe hypertension and not restarted until the condition has been adequately evaluated and treated.

The safety of ALERTEC 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, such as myocardial infarction, have been reported in patients with and without a history of cardiovascular disease while being treated with ALERTEC. In some of these cases there was a close temporal association to the use of ALERTEC. The risks of using ALERTEC 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 cardiac evaluation, including an electrocardiogram (ECG), be considered for such patients prior to treatment.

Furthermore, in clinical studies of modafinil, signs and symptoms including chest pain, palpitations, dyspnea, 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 ALERTEC not be used in patients with a history of left ventricular hypertrophy or in patients with ischemic ECG changes, chest pain, arrhythmia, or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Such signs may 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.

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

Blood pressure monitoring in short-term (<3 months) controlled trials showed no clinically significant changes in mean systolic and diastolic blood pressure in patients receiving ALERTEC compared to placebo. However, a retrospective analysis of the use of antihypertensive medication in these studies showed that a greater proportion of patients on ALERTEC required new or increased use of antihypertensive medications (2.4%) compared to patients on placebo (0.7%). The differential was slightly larger when only studies on OSA were included, with 3.4% of patients on ALERTEC and 1.1% of patients on placebo requiring such alterations in the use of antihypertensive medication.

Cardiovascular adverse reactions increase significantly after single doses of 300mg and after total daily doses of more than 400mg.

Use in Combination with OtherCNS Stimulants

Caution should be taken when ALERTEC is used in combination with amphetamines or other similar CNS stimulants, such as methylphenidate. Some CNS stimulants may cause increases in blood pressure and heart rate, and the concomitant use of these drugs may result in additive effects. Clinically important prolongation of the QTc interval may also occur within a few hours after simultaneous administration of modafinil and dextroamphetamine. ALERTEC and other CNS stimulants should not be taken at the same time. (see **Drug Interactions**).

Patients using Steroidal Contraceptives

The effectiveness of steroidal contraceptives may be reduced when used with ALERTEC and for one month after discontinuation of therapy (see **Drug Interactions**). Alternative or concomitant methods of contraception other than steroidal are recommended for patients treated with ALERTEC, and for one month after discontinuation of ALERTEC.

Patients Using Cyclosporine

The blood levels of cyclosporine may be reduced when used with ALERTEC (see **Drug Interactions**). Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustment for cyclosporine should be considered when these drugs are used concomitantly.

Carcinogenesis and Mutagenesis

Please refer to the **Toxicology** section for animal data.

Dependence/Tolerance

The potential for abuse should be considered when prescribing ALERTEC (see **Action and Clinical Pharmacology, Mechanism of Action** for pre-clinical results). 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 (e.g., incrementation of doses or drug-seeking behavior).

In a study of 24 subjects with polysubstance abuse histories, ALERTEC doses of 200, 400, and 800mg modafinil produced psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of CNS stimulants versus placebo but showed lower abuse potential relative to methylphenidate (45 and 90mg). ALERTEC did not produce a significant amphetamine score on the Addiction Research Center Inventory (ARCI) questionnaire. ALERTEC was also clearly distinguishable from amphetamine on this scale in a study of 300mg in 16 healthy volunteers. Subjective effects of ALERTEC differed markedly from those induced by 15mg of *d*-amphetamine, and to a lesser extent, from those seen with placebo.

Withdrawal

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

Endocrine and Metabolism

ALERTEC may cause induction of hepatic microsomal enzymes, especially at doses greater than 400mg. The metabolism of oral anticoagulants, antidepressant, anticonvulsants, and oral contraceptives may be increased. Patients should be monitored closely for changes in their response to any of these therapies when treatment with ALERTEC is either initiated or discontinued.

Hepatic/Biliary/Pancreatic

Severe Hepatic Impairment

In patients with severe hepatic impairment with cirrhosis (see **Action and Clinical Pharmacology**), the oral clearance of modafinil was decreased by about 60% and the steady state was doubled compared to normal patients. ALERTEC should be administered at a reduced dose in patients with severe hepatic impairment (see **Dosage and Administration**).

Liver Function Tests

In Phase 1, 2, and 3 studies, mean plasma levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (AP) were found to be higher following administration of ALERTEC, but not placebo. Few subjects, however, had GGT or AP elevations outside of the normal range. Shifts to higher, but not clinically significantly abnormal, GGT and AP values appeared to increase with time in the population treated with ALERTEC in the Phase 3 clinical trials. No differences were apparent in alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin.

Neurologic

Central nervous system adverse reactions increase significantly after single doses of 300mg and after total daily doses of more than 400mg.

Renal

Severe Renal Impairment

There is inadequate information to determine the safety and efficacy of dosing in patients with severe renal impairment.

In a single dose 200mg modafinil study, compared to healthy individuals, modafinil plasma concentrations were unchanged in patients with severe chronic renal failure (creatinine clearance ≤20mL/min). However, the renal clearance of the active metabolite, modafinil acid, was reduced, leading to a 9-fold increase in exposure. No adverse events were reported in this small number of patients. The clinical significance of increased modafinil acid plasma concentrations is unknown.

Sexual Function/Reproduction

Please refer to the **Toxicology** section for animal data.

Special Populations

Pregnant Women: In studies conducted in rats and rabbits, development toxicity was observed at clinically relevant exposures. Embryotoxicity was observed in the absence of maternal toxicity when rats received oral modafinil (50, 100, or 200mg/kg/day) throughout the period of organogenesis. At a dose 5 times the maximum recommended daily human dose of 400mg on a mg/m^2 basis, there was an increase in resorption, hydronephrosis and skeletal variations. The higher no-effect dose for rat embryofetal developmental toxicity was associated with a plasma modafinil exposure approximately 0.25 to 0.5 times the AUC in humans at the recommended daily dose (RHD) of 200 to 400mg. However, in a subsequent study of up to 480mg/kg/day (plasma modafinil exposure approximately 1-2 times the AUC in humans at the RHD) no adverse effects on embryofetal development were observed.

Modafinil administered orally to pregnant rabbits throughout the period of organogenesis at doses of 45, 90, and 180mg/kg/day increased the incidences of fetal structural alterations and embryofetal death at the highest dose. The highest no-effect dose for developmental toxicity was associated with a plasma modafinil AUC approximately equal to the AUC in humans at the RHD. Oral administration of armodafinil (the R-enantiomer of modafinil – not approved in Canada; 60, 200, or 600mg/kg/day) to pregnant rats throughout the period of organogenesis resulted in increased incidences of fetal visceral and skeletal variations at the intermediate dose or greater and decreased fetal body weights at the highest dose. The no-effect dose for rat embryofetal developmental toxicity was associated with a plasma armodafinil exposure (AUC) approximately one-tenth times the AUC for armodafinil in humans treated with modafinil at the RHD.

Modafinil administration to rats throughout gestation and lactation at oral doses of up to 200mg/kg/day resulted in decreased viability in the offspring at doses greater than 20mg/kg/day (plasma modafinil AUC approximately 0.05 to 0.1 times the AUC in humans at the RHD). No effects on postnatal developmental and neurobehavioral parameters were observed in surviving offspring**.**

There are no adequate and well-controlled studies in pregnant women. Two cases of intrauterine growth retardation and one case of spontaneous abortion have been reported in association with armodafinil (the R-enantiomer of modafinil; not marketed in Canada) and modafinil. Although the pharmacology of modafinil and armodafinil is not identical to that of the sympathomimetic amines, they do share some pharmacologic properties with this class. Certain of these drugs have been associated with intrauterine growth retardation and spontaneous abortions. Whether the cases reported are drug-related is unknown.

ALERTEC is not recommended during pregnancy.

The effect of modafinil on labor and delivery in humans has not been systematically investigated.

Nursing Women: Modafinil may be excreted in human milk. In rats, peak ^{14}C-modafinil concentrations appeared in the milk of lactating animals within one hour and at levels similar to the ones found in plasma. ALERTEC is therefore not recommended during lactation.

Pediatrics (<18 years of age): Safety and effectiveness in pediatric patients have not been established. Serious skin rashes, including erythema multiforme major (EMM) and Stevens-Johnson Syndrome (SJS), have been associated with modafinil use in pediatric patients (see **Warnings and Precautions, Serious Rash, Including Stevens-Johnson Syndrome**).

ALERTEC is not approved for use in pediatric patients for any indication including Attention Deficit Hyperactivity Disorder.

In a controlled 6-week study, 165 pediatric patients (aged 5-17 years) with narcolepsy were treated with modafinil (n=123), or placebo (n=42). There were no statistically significant differences favoring modafinil over placebo in prolonging sleep latency as measured by MSLT, or in perceptions of sleepiness as determined by the Clinical Global Impression - Clinician scale (CGI-C).

In the controlled and open-label clinical studies, treatment emergent adverse events of the psychiatric and nervous system included Tourette's syndrome, insomnia, hostility, increased cataplexy, increased hypnagogic hallucinations and suicidal ideation. Transient leucopenia, which resolved without medical intervention, was also observed. In the controlled clinical study, 3 of 38 girls, ages 12 or older, treated with modafinil experienced dysmenorrhea compared to 0 of 10 girls who received placebo.

Geriatrics: Dyskinesias have been reported in the elderly with the use of ALERTEC. Elimination of modafinil and its metabolites may be reduced as a consequence of aging, and elderly patients have been found to be more sensitive to the effects of ALERTEC; these patients should be started at a lower dose. Caution should also be exercised when coadministration of modafinil and clomipramine is deemed necessary (see **Drug Interactions**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most commonly observed adverse events (≥5%) associated with the use of ALERTEC and observed more frequently than placebo-treated patients in the placebo-controlled clinical studies in primary disorders of sleep and wakefulness were headache, nausea, rhinitis, nervousness, diarrhea, back pain, anxiety, dizziness, dyspepsia, and insomnia. The adverse event profile was similar across these studies.

In the placebo-controlled clinical trials, 74 of the 934 patients (8%) who received ALERTEC 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 ALERTEC than placebo patients were headache (2%), anxiety, chest pain, dizziness, insomnia, nausea and nervousness (each <1%).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The following table presents the adverse experiences that occurred at a rate of 1% or more and were more frequent in adult patients treated with ALERTEC than in placebo-treated patients in the principal, placebo-controlled clinical trials.

Table 1. Incidence of Treatment-Emergent Adverse Experiences in Parallel-Group, Placebo-controlled Clinical Trials[1] with ALERTEC in Adults with Narcolepsy and Obstructive Sleep Apnea and Circadian Rhythm Sleep Disorder, Shift Work Type (Shift Work Disorder) (200mg, 300mg and 400mg)*

	Modafinil n=934 (%)	Placebo n=567 (%)
Body as Whole		
Headache	34%	23%
Back Pain	6%	5%
Flu Syndrome	4%	3%
Chest Pain	3%	1%
Chills	1%	0%
Neck Rigidity	1%	0%
Cardiovascular		
Hypertension	3%	1%
Tachycardia	2%	1%
Palpitation	2%	1%
Vasodilatation	2%	0%

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	Modafinil n=934 (%)	Placebo n=567 (%)
Digestive		
Nausea	11%	3%
Diarrhea	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%
Hemic/Lymphatic		
Eosiniphilia	1%	0%
Metabolic/Nutritional		
Edema	1%	0%
Nervous		
Nervousness	7%	3%
Insomnia	5%	1%
Anxiety	5%	1%
Dizziness	5%	4%
Depression	2%	1%
Paresthesia	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%

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	Modafinil n=934 (%)	Placebo n=567 (%)
Urogenital		
Urine Abnormality	1%	0%
Hematuria	1%	0%
Pyuria	1%	0%

* Six double-blind, placebo controlled clinical studies in narcolepsy (200 and 400mg), OSA (200 and 400mg) and SWD (200mg and 300mg).

1 Events reported by at least 1% of patients treated with ALERTEC 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 ALERTEC incidence was at least 1%, but equal to or less than placebo are not listed in the table. These events included the following: abdominal pain, abnormal electrocardiogram, accidental injury, allergic reaction, arthritis, asthenia, bronchitis, cataplexy, conjunctivitis, dysmenorrhea[4], dyspnea, ear pain, ecchymosis, fever, increased appetite, increased cough, infection, hyperglycemia, hypotension, hypothermia, leg cramps, migraine, myalgia, neck pain, pain, periodontal abscess, peripheral edema, rash, sinusitis, sleep disorder, thinking abnormality, tooth disorder, weight gain, weight loss, urinary tract infection, viral infection, vomiting.

2 Elevated liver enzymes.

3 Oro-facial dyskinesias.

4 Incidence adjusted for gender.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

In the narcolepsy pivotal clinical trials, adverse events occurring less frequently were:

Nervous system: CNS stimulation (1.0%), and twitch (0.7%).
Skin and appendages: pruritus (1.0%).
Special senses: conjunctivitis (1.0%).
Urogenital system: urinary frequency (0.7%).

Adverse events reported only once in the narcolepsy pivotal clinical trials include:

Body as a whole: jaw pain (0.3%) and photosensitivity (0.3%).
Cardiovascular system: heart arrest (0.3%).
Digestive system: saliva increase (0.3%).
Hemic and lymphatic system: leukocytosis (0.3%).
Musculoskeletal system: myasthenia (0.3%).
Nervous system: ataxia (0.3%), coordination abnormality (0.3%), dream abnormality (0.3%), libido increase (0.3%), personality disorder (0.3%).
Special senses: decreased hearing (0.3%), hyperacusis (0.3%).
Urogenital system: cystitis (0.3%), and impotence (0.3%).

Dose Dependency of Adverse Events

In the adult placebo-controlled clinical trials which compared doses of 200, 300, and 400mg/day of ALERTEC and placebo, the only adverse events that were clearly dose related were headache and anxiety.

Vital Sign Changes

While there was no consistent change in mean values of heart rate or systolic and diastolic blood pressure, the requirement for antihypertensive medication was slightly greater in patients on ALERTEC compared to placebo.

Weight Changes

There were no clinically significant differences in body weight change in patients treated with ALERTEC compared to placebo-treated patients in the placebo-controlled clinical trials.

Laboratory Changes

Clinical chemistry, hematology, and urinalysis parameters were monitored in Phase 1, 2, and 3 studies. In these studies, mean plasma levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (AP) were found to be higher following administration of ALERTEC, but not placebo. Few subjects, however, had GGT or AP elevations outside of the normal range. Shifts to higher, but not clinically significantly abnormal, GGT and AP values appeared to increase with time in the population treated with ALERTEC in the Phase 3 clinical trials. No differences were apparent in alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin.

ECG Changes

No treatment-emergent pattern of ECG abnormalities was found in placebo-controlled clinical trials following administration of ALERTEC. 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 (300mg/day in divided doses). (see **Warnings and Precautions**, **Cardiovascular**).

<u>Post-Market Adverse Drug Reactions</u>

In addition to the adverse events observed during clinical trials, the following adverse events have been identified during post-approval use of ALERTEC in clinical practice. Because these adverse effects are reported voluntarily from a population of uncertain size, reliable estimates of their frequency cannot be made.

Hematologic: agranulocytosis. The causality of the two cases reported could not be established due to concomitant use of Dyazide® (hydrochlorothiazide/triamterene) in the first case and of omeprazole in the second case.

Central nervous system: irritability, psychomotor hyperactivity, symptoms of mania, symptoms of psychosis

Hypersensitivity: anaphylactic reaction, angioedema, urticaria (hives)

Dermatologic: rare reports of serious skin reactions [including cases of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), erythema multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis].

Cardiovascular: cardiac arrhythmias (including atrial fibrillation, conduction abnormalities, and premature ventricular contraction), ischaemic heart disease (including angina pectoris and myocardial infarction).

DRUG INTERACTIONS

Drug-Drug Interactions

CNS Active Drugs

Methylphenidate - In a single-dose study in 21 healthy male volunteers, aged 21-37 years, co-administration of modafinil (200mg) with methylphenidate (40mg) did not cause any significant alterations in the pharmacokinetics of either drug. However, the absorption of modafinil may be delayed by approximately one hour when co-administered with methylphenidate. In a subsequent study, the effects of methylphenidate (20mg per day) at steady state on the pharmacokinetics of modafinil (400mg per day) at steady state were examined, with administration of the stimulant 8 hours after the daily dose of modafinil. No effects on the pharmacokinetic parameters of modafinil were observed.

Dextroamphetamine - In a single-dose study in healthy volunteers, simultaneous administration of modafinil (200mg) with dextroamphetamine (10mg) did not cause any significant alterations in the pharmacokinetics of either drug. However, the absorption of ALERTEC may be delayed by approximately one hour when co-administered with dextroamphetamine. In a subsequent study, the effects of dextroamphetamine (20mg per day) at steady state on the pharmacokinetics of modafinil (400mg per day) at steady state were examined, with administration of the stimulant 7 hours after the daily dose of modafinil. No effects on the pharmacokinetic parameters of modafinil were observed. In the single-dose study, blood pressure and pulse rate were increased at a greater extent after administration of the two drugs combined than after administration of either drug alone. A mean increase in QTc interval of 15 msec, and individual prolonged QTc interval (including one result of clinical importance = 507 ms) were also observed 2 hours after simultaneous administration of the two drugs at their minimum recommended dosage (see **Warnings and Precautions**). The same patient had a prolonged QTc interval of 480 ms when dexamphetamine was administered alone.

Patients who are receiving ALERTEC with drugs with CNS activity should be monitored closely (see **Warnings and Precautions**).

Clomipramine - In 18 healthy, male volunteers, aged 22-44 years, the co-administration of a single dose of clomipramine (50mg) on the first of three days of treatment with modafinil (200mg/day) did not appear to affect the pharmacokinetics of either drug. However, systolic blood pressure was significantly higher when the two drugs were administered together than following administration of either drug alone [mean increase above baseline 12.4mmHg (combination) vs 5.7mmHg (modafinil alone) vs 6.4mmHg (clomipramine alone)]. Also, one incident of increased levels of clomipramine and its active metabolite desmethylclomipramine has been reported in a patient with narcolepsy during treatment with modafinil. The hypertensive effects of co-administration of higher than 50mg doses of clomipramine and multiple doses of modafinil (200-400mg daily) is unknown. Therefore, caution should be exercised when co-administration of modafinil and clomipramine is deemed necessary (see **Warnings and Precautions**).

Triazolam - In a pharmacodynamic study, single doses of modafinil (50, 100 or 200mg) and triazolam (0.25mg) were given to healthy, male volunteers, aged 19-26 years. No clinically important alterations in the safety profile of modafinil or triazolam were noted. However, the effect of concomitant administration of multiple doses of modafinil (200-400mg daily) and 0.25mg triazolam is unknown. In the drug interaction study between ALERTEC and ethinyl estradiol (EE_2), on the same days as those for the plasma sampling for EE_2 pharmacokinetics, a single dose of triazolam (0.125mg) was also administered. Mean C_{max} and $AUC_{0-\infty}$ of triazolam were decreased by 42% and 59%, respectively, and its elimination half-life was decreased by approximately an hour after the modafinil treatment. Dosage adjustment for triazolam may be needed.

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 modafinil.

Other Drugs

Warfarin - The following changes were observed in the pharmacokinetic profiles of S-warfarin: no changes in mean C_{max}, 20% increase in mean AUC for S-warfarin, in 13 healthy subjects given a single dose of racemic warfarin (5mg) following chronic administration of modafinil (200mg/day for 7 days followed by 400mg/day for 27 days) relative to the profiles in 12 subjects given placebo. However, because multiple doses of warfarin in patients were not evaluated, the relevance of these findings in a clinical setting is unknown. For this reason, more frequent evaluations of prothrombin times/INR than the regular monitoring is advisable whenever ALERTEC is co-administered with warfarin.

Oral contraceptives - Administration of modafinil to 16 female volunteers once daily at 200mg/day for 7 days followed by 400mg/day for 21 days resulted in a mean 11% decrease in C_{max} and 18% decrease in AUC_{0-24} of ethinyl estradiol (EE_2; 0.035mg; administered orally with norgestimate). There was no apparent change in the elimination rate of ethinyl estradiol. However, higher individual decreases in the AUC_{0-24} of ethinyl estradiol and increased incidence of metrorrhagia were observed when modafinil and ethinyl estradiol were administered concomitantly. Also, one woman in the study had a decrease of 54% in the AUC_{0-24} of ethinyl estradiol during concomitant modafinil treatment. She had a negative pregnancy test at study completion, and a positive pregnancy test 25 days after she completed the study. She thereafter was lost to follow-up and further information on her pregnancy is not available (see **Warnings and Precautions**).

Cyclosporine - One case of an interaction between modafinil and cyclosporine, a substrate of CYP3A4, has been reported in a 41 years old woman who had undergone an organ transplant. After one month of administration of 200mg/day of modafinil, cyclosporine blood levels were decreased by 50%. The interaction was postulated to be due to the increased metabolism of cyclosporine, since no other factor expected to affect the disposition of the drug had changed. Dosage adjustment for cyclosporine may be needed.

Concomitant use of ALERTEC and other agents that may elevate blood pressure has not been evaluated. Caution should be exercised when prescribing ALERTEC to patients already taking such agents.

Multi-dose treatment (twice daily, one at 8 a.m. and one at noon) with ALERTEC at 400mg/day or higher for 7 days was shown to decrease the half-life of antipyrine. This finding suggests that chronic administration of ALERTEC at 400mg or higher daily may induce the metabolism of other drugs.

Based on in vitro data, modafinil is metabolized partially by the 3A isoform subfamily of hepatic cytochrome P450 (CYP3A4). In addition, modafinil has the potential to inhibit CYP2C19, suppress CYP2C9, and induce CYP3A4, CYP2B6, and CYP1A2. Because modafinil and modafinil sulfone are reversible inhibitors of the drug-metabolizing enzyme CYP2C19, co-administration of modafinil with drugs such as diazepam, propranolol, phenytoin, or S-mephenytoin, which are largely eliminated via that pathway, may increase the circulating levels of those compounds and may require dosage reduction and monitoring for toxicity. In addition, in individuals deficient in the enzyme CYP2D6 (i.e., 7-10% 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. An in vitro study demonstrated that armodafinil (one of the enantiomers of modafinil; not marketed in Canada) is a substrate of P-glycoprotein.

ALERTEC has a slight induction effect at the concentration of 10^{-5}M on CYP 3A, a hepatic enzyme associated with the metabolism of oral contraceptives. Chronic administration of modafinil 400mg per day was found to decrease the systemic exposure to two CYP3A4 substrates, ethinyl estradiol and triazolam, after oral administration suggesting that CYP3A4 had been induced. Caution is therefore recommended with the combination of oral contraceptives and ALERTEC (see **Warnings and Precautions**). Chronic administration of modafinil can increase the elimination of substrates of CYP3A4. Dosage adjustment should be considered for concomitant medications that are substrates for CYP3A4, such as triazolam and cyclosporine.

In vitro studies using liver microsomes suggest that formation of the metabolite modafinil sulfone is primarily catalyzed by cytochrome CYP 3A. Potential inhibitors such as itraconazole or ketoconazole may therefore reduce the formation of modafinil sulfone. Because this pathway is of relatively minor importance in humans, such an interaction would not be expected to appreciably alter modafinil elimination.

The exposure of human hepatocytes to modafinil in vitro produced an apparent concentration-related suppression of expression of CYP2C9 activity suggesting that there is a potential for a metabolic interaction between modafinil and the substrates of this enzyme (e.g., S-warfarin and phenytoin). In a subsequent clinical study in healthy volunteers, chronic modafinil treatment resulted in a 20% increase in mean AUC on the single-dose pharmacokinetics of S-warfarin when compared to placebo (see **Drug Interactions**).

It should be noted that evaluation of drug interactions based on in vitro systems may 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.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The safety and efficacy of modafinil in children under the age of 18 years has not been established. Therefore, modafinil is not indicated for use in pediatric patients (see Indications and Clinical Use, Pediatrics; Warnings and Precautions, Serious Rash, including Stevens-Johnson Syndrome).

Dosage adjustment should be considered for concomitant medications that are substrates for CYP3A4, such as triazolam and cyclosporine.

Because modafinil and modafinil sulfone are reversible inhibitors of the drug-metabolizing enzyme CYP2C19, co-administration of modafinil with drugs such as diazepam, propranolol, phenytoin, or S-mephenytoin, which are largely eliminated via that pathway, may increase the circulating levels of those compounds may have prolonged elimination upon co-administration with ALERTEC and may require dosage reduction and monitoring for toxicity.

Elderly: In elderly patients, elimination of ALERTEC 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 **Warnings and Precautions**; **Action and Clinical Pharmacology**).

Severe Hepatic Impairment: In patients with severe hepatic impairment, the dose of ALERTEC should be reduced to one-half of the usual recommended dose (see **Warnings and Precautions**).

Recommended Dose and Dosage Adjustment

Narcolepsy

The adult daily dosage of ALERTEC (modafinil) for patients with narcolepsy is between 200 to 400mg, divided between morning and noon doses. The initial daily dose should be 200mg in divided doses, increasing in increments of 100mg as needed and tolerated.

The total daily dose can be divided according to the needs and response of the patient. The timing should be aimed to coincide with the periods of greatest excessive daytime sleepiness. The second dose should generally be taken no later than the early afternoon to minimize the risk of insomnia.

Although the occasional patient may need and tolerate daily doses of 500mg, limited data from trials in healthy volunteers suggest that the number and type of side effects increase significantly after single doses of 300mg and after total daily doses of more than 400mg, compared to 100 and 200mg doses b.i.d. Single doses of 300mg or more, or total daily doses of more than 400mg are therefore not recommended.

Obstructive Sleep Apnea

In OSA, ALERTEC is indicated as an adjunct to successful standard treatment(s) for the underlying obstruction (see **Warnings and Precautions**). For patients with OSA, the adult daily dosage of ALERTEC is 200mg taken as a single dose in the morning.

Circadian Rhythm Sleep Disorder, Shift Work Type (*Shift Work Disorder)*

For patients with SWD, the adult daily dosage of ALERTEC is 200mg taken approximately 1 hour prior to the start of their work shift.

Missed Dose

If a dose is missed, it can be taken when remembered, unless it is close to the time for the next dose. Taking the medication in the evening or the late afternoon may prevent from falling asleep at usual bedtime, and should, therefore, be avoided.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms most often accompanying ALERTEC 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.

Intentional overdose by patients have been reported, where death has occurred with modafinil, either alone (dose 72 grams) or in combination with other drugs (dose from 200mg up to 6000mg).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Modafinil is a central nervous system stimulant.

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

EEG studies in man showed that modafinil increases high frequency α waves and decreases δ and θ waves, an effect consistent with increased alertness. When taken in the evening, modafinil 200mg increases sleep latency and decreases total sleep time. Modafinil has weak peripheral sympathomimetic activity: single doses of 200mg and total daily doses of 400mg have minimal effect on hemodynamics. Higher doses cause blood pressure and heart rate to increase in a dose-dependent manner.

In addition to its wake-promoting effects and ability to increase locomotor activity in animals, modafinil in humans produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants.

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 adult 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 200-600mg/day once daily in healthy volunteers. Apparent steady states of total modafinil and *l*-(-)-modafinil are reached after 2-4 days of dosing.

Absorption: Absorption of ALERTEC tablets is rapid, with peak plasma concentrations occurring at 2-4 hours. The bioavailability of ALERTEC tablets is approximately equal to that of an aqueous suspension. The absolute oral bioavailability was not determined due to the aqueous insolubility (<1mg/mL) of modafinil, which precluded intravenous administration.

The C_{max} is slightly lower and the t_{max} slightly longer when ALERTEC is given after a meal but has no effect on overall ALERTEC bioavailability. Both the area under the plasma concentration curve (AUC) and the peak plasma concentration showed dose-proportionality in the 50 to 400mg range.

Distribution: Modafinil is well distributed in body tissue with an apparent volume of distribution (~0.9L/kg) larger than the volume of total body water (0.6L/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 200mg/day, modafinil exhibits no displacement of protein binding of warfarin, diazepam or propranolol. Even at much larger concentrations (1000μM; >25 times the C_{max} of 40μM at steady state at 400mg/day), modafinil has no effect on warfarin binding. Modafinil acid at concentrations >500μM decreases the extent of warfarin binding, but these concentrations are >35 times those achieved therapeutically.

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

Metabolism occurs through hydrolytic deamination, S-oxidation, aromatic ring hydroxylation, and glucuronic conjugation. Following oral administration of modafinil, less than 10% of the dose is found unchanged in the urine. In a clinical study using radiolabeled 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 feces). 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 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 affects of modafinil.

In adults, decreases in trough levels of modafinil have sometimes been observed after multiple weeks of dosing, suggesting auto-induction, but the magnitude of the decreases and the inconsistency of their occurrence suggest that their clinical significance is minimal. Significant accumulation of modafinil sulfone has been observed after multiple doses due to

its long elimination half-life of 40 hours. Induction of metabolizing enzymes, most importantly cytochrome P-450 (CYP) 3A4, has also been observed in vitro after incubation of primary cultures of human hepatocytes with modafinil and in vivo after extended administration of modafinil at 400mg/day. (For further discussion of the effects of modafinil on CYP enzyme activities, see **Drug Interactions**).

Special Populations and Conditions

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

Age Effect: A slight decrease (~20%) in the oral clearance (CL/F) of modafinil was observed in a single dose study at 200mg in 12 subjects with a mean age of 63 years (range 53-72 years), but the change was considered not likely to be clinically significant. In a multiple dose study (300mg/day) in 12 patients with a mean age of 82 years (range 67-87 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 Administration)**.

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

Renal Impairment: In a single dose 200mg modafinil study, severe chronic renal failure (creatinine clearance ≤20mL/min) did not significantly influence the pharmacokinetics of modafinil, but exposure to modafinil acid (an active metabolite) was increased 9-fold (see **Warnings and Precautions**).

Severe Hepatic Impairment: Pharmacokinetics and metabolism were examined in patients with cirrhosis of the liver (6 males and 3 females). Three patients had stage B or B+ cirrhosis (per the Child 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 ALERTEC should be reduced in patients with hepatic impairment (see **Warnings and Precautions**).

STORAGE AND STABILITY

Store between 15° and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each white to off-white capsule shaped tablet of ALERTEC, debossed with "100" on one

side, contains modafinil 100mg. Available in blister strips of 10 tablets, in packages of three strips.

Nonmedicinal Ingredients: Lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, sodium croscarmellose

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

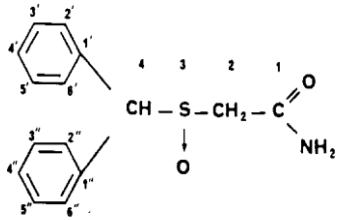
Drug Substance

Proper name: Modafinil

Chemical name: 2-[(diphenylmethyl)sulphinyl] acetamide

Molecular formula and molecular mass: $C_{15}H_{15}NO_2$ S 273.35

Structural formula:



Physicochemical properties: Practically insoluble in water; sparingly soluble in acetone and methanol, slightly soluble in ethanol and chloroform.

Melting Point: 162°C

Physical Form: White crystalline powder

CLINICAL TRIALS

The effectiveness of ALERTEC in reducing excessive sleepiness has been established in the following sleep disorders: narcolepsy, obstructive sleep apnea (OSA) and circadian rhythm sleep disorder, sleep work type (shift work disorder) (SWD).

Narcolepsy

The effectiveness of ALERTEC in reducing the excessive sleepiness (ES) associated with narcolepsy was established in two 9-week, multicenter, 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 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 behaviors, 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 (MSLT) with two or more sleep onset REM periods, and the absence of any other clinically significant active medical or psychiatric disorder. The MSLT, an objective daytime polysomnographic assessment of the patient's ability to fall asleep in an unstimulating environment, measures latency (in minutes) to sleep onset averaged over 4 test sessions at 2-hour intervals following nocturnal polysomnography. 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 15 minutes after sleep onset.

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). For a successful trial, both measures had to show significant improvement.

The MWT measures latency (in minutes) to sleep onset averaged over 4 test sessions at 2-hour intervals following nocturnal polysomnography. For each test session, the subject was asked to attempt to remain awake without using extraordinary measures. Each test session was terminated after 20 minutes if no sleep occurred or 10 minutes 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.* Patients were rated by evaluators who had no access to any data about the patients other than a measure of their baseline severity. Evaluators were not given any specific guidance about the criteria they were to apply when rating patients.

Other assessments of effect included the Multiple Sleep Latency Test (MSLT), Epworth Sleepiness Scale (ESS; a series of questions designed to assess the degree of sleepiness in everyday situations) the Steer Clear Performance Test (SCPT; a computer-based evaluation of a patient's ability to avoid hitting obstacles in a simulated driving situation), standard nocturnal polysomnography, and patient's daily sleep log. Patients were also assessed with the Quality of Life in Narcolepsy (QOLIN) scale, which contains the validated SF-36 health questionnaire.

Both studies demonstrated improvement in objective and subjective measures of excessive daytime sleepiness for both the 200mg and 400mg doses compared to placebo. Patients treated with either dose of ALERTEC showed a statistically significantly enhanced ability to remain awake on the MWT (all p values <0.00l) at Weeks 3, 6, 9, and final visit compared to placebo and a statistically significantly greater global improvement, as rated on the CGI-C scale (all p values <0.05).

The average sleep latencies (in minutes) on the MWT at baseline for the 2 controlled trials are shown in Table 2 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 two clinical trials are shown in Table 3 below.

Similar statistically significant treatment-related improvements were seen on other measures of impairment in narcolepsy, including a patient assessed level of daytime sleepiness on the ESS ($p<0.001$ for each dose in comparison to placebo).

Nighttime sleep measured with polysomnography was not affected by the use of ALERTEC.

Obstructive Sleep Apnea (OSA)

The effectiveness of ALERTEC in reducing the excessive sleepiness associated with OSA was established in two clinical trials. In both studies, patients were enrolled who met the International Classification of Sleep Disorders (ICSD) criteria for OSA (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 apneas, 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 apneas, bradytachycardia, and arterial oxygen desaturation in association with the apneas. 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 apnea/hypopnea was required along with documentation of CPAP use.

In the first study, a 12-week multicenter placebo-controlled trial, a total of 327 patients were randomized to receive ALERTEC 200mg/day, ALERTEC 400mg/day, or matching placebo. The majority of patients (80%) were fully compliant with CPAP, defined as CPAP use >4 hours/night on >70% nights. The remainder were partially CPAP compliant, defined as CPAP use <4 hours/night on >30% nights. CPAP use continued throughout the study. 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 Week 12 or the final visit.

Patients treated with ALERTEC showed a statistically significant improvement in the ability to remain awake compared to placebo-treated patients as measured by the MWT ($p<0.001$) at endpoint [Table 2]. ALERTEC-treated patients also showed a statistically significant improvement in clinical condition as rated by the CGI-C scale ($p<0.001$) [Table 3]. The two doses of ALERTEC performed similarly.

In the second study, a 4-week multicenter placebo-controlled trial, 157 patients were randomized to either ALERTEC 400mg/day or placebo. Documentation of regular CPAP use (at least 4 hours/night on 70% of nights) was required for all patients.

The primary outcome measure was the change from baseline on the ESS at Week 4 or final visit. The baseline ESS scores for the ALERTEC and placebo groups were 14.2 and 14.4, respectively. At Week 4, the ESS was reduced by 4.6 in the ALERTEC group and by 2.0 in the placebo group, a difference that was statistically significant ($p<0.0001$).

Nighttime sleep measured with polysomnography was not affected by the use of ALERTEC.

Circadian Rhythm Sleep Disorder, Shift Work Type (Shift Work Disorder) (SWD)

The effectiveness of ALERTEC for the excessive sleepiness associated with SWD was demonstrated in a 12-week placebo-controlled clinical trial. A total of 209 patients with chronic SWD were randomized to receive ALERTEC 200mg/day or placebo. All patients met the International Classification of Sleep Disorders (ICSD-10) criteria for chronic SWD (which are consistent with the American Psychiatric Association DSM-IV 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.

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 SWD. 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 Week 12 or the final visit and 2) the change in the patient's overall disease status, as measured by the Clinical Global Impression of Change (CGI-C) at Week 12 or the final visit. Patients treated with ALERTEC showed a statistically significant prolongation in the time to sleep onset compared to placebo-treated patients, as measured by the night-time MSLT ($p<0.05$). Improvement on the CGI-C was also observed to be statistically significant ($p<0.001$).

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

Table 2. Average Baseline Sleep Latency and Change from Baseline at Final Visit in Adults (MWT and MSLT in minutes)

Disorder	Measure	ALERTEC 200mg*		ALERTEC 400mg*		Placebo	
		Baseline	Change from Baseline	Baseline	Change from Baseline	Baseline	Change from Baseline
Narcolepsy I	MWT	5.8	2.3	6.6	2.3	5.8	-0.7
Narcolepsy II	MWT	6.1	2.2	5.9	2.0	6.0	-0.7
OSA	MWT	13.1	1.6	13.6	1.5	13.8	-1.1
SWD	MSLT	2.1	1.7	-	-	2.0	0.3

* Significantly different than placebo for all trials ($p<0.01$ for all trials but SWD, which was $p<0.05$)

Table 3. Clinical Global Impression of Change (CGI-C) (Percent of Adult Patients Who Improved at Final Visit)

Disorder	ALERTEC 200mg*	ALERTEC 400mg*	Placebo
Narcolepsy I	64 %	72 %	37 %
Narcolepsy II	58 %	60 %	38 %
OSA	61 %	68 %	37 %
SWD	74 %	-	36 %

* Significantly different than placebo for all trials ($p<0.01$)

Comparative Bioavailability Study

A randomized crossover comparative bioavailability study was performed on twenty-four (24) healthy adult male volunteers under fasting conditions to evaluate a change in formulation of ALERTEC with changes in the nonmedicinal ingredients (with or without magnesium

monosilicate). The results from measured data following a single administration of a 200mg dose (2 x100mg tablets) of test and reference products are summarized in Table 4.

Table 4. Modafinil (2 x 100mg) From Measured Data – Healthy Subjects Under Fasting Conditions

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval of Ratio of Geometric Means
AUC_T (μg•hr/mL)	52.0[#] 53.5 (24.6) [€]	53.8[#] 55.4 (24.7) [€]	96.6	(93.0; 100.3)
AUC_I (μg•hr/mL)	56.4[#] 58.1 (25.5) [€]	58.5[#] 60.4 (26.1) [€]	96.3	(93.2; 99.4)
C_{MAX} (μg/mL)	4.5[#] 4.6 (20.5) [€]	4.5[#] 4.6 (17.4) [€]	98.7	(93.0; 104.8)
T_{MAX}[§] (h)	2.0 (0.5, 4)	2.0 (0.5, 4)		
$T_{½}$[ϕ] (h)	12.4 (3.00)	13.5 (3.73)		

* Tablets formulated without magnesium monosilicate.
† Tablets formulated with magnesium monosilicate.
[#] Expressed as the geometric mean.
[€] Expressed as the arithmetic mean (Coefficient of Variation % - CV%)
[§] Expressed as median (range).
[ϕ] Expressed as the arithmetic mean (Standard Deviation - SD).

DETAILED PHARMACOLOGY

Increased Wakefulness

The administration of modafinil increases the spontaneous locomotor activity after single or repeated dosing in animals. After oral or intraperitoneal administration in mice, modafinil induced an increase of 45% (16mg/kg) to 173% (256mg/kg) in locomotion after one hour. No agitation, stereotypy, or convulsions were observed. The intensity and duration of action of the increased locomotion, were directly related to the blood concentration of modafinil. Repeat oral administration from 4 to 18 days maintained the induction of hyperactivity of the animals; this effect however could be reduced by up to 25% due to the liver enzymatic induction caused by modafinil.

The modafinil "increased wakefulness" can also be shown in other mouse models. In the behavioral despair test, modafinil progressively decreased the duration of immobilization from 45% (8mg/kg IP) to 95% (128mg/kg IP). Modafinil reduced the

duration of sleep induced by barbital. A reduction in sleep duration of 47% and 78% was recorded in mice treated with 16mg and 64mg/kg of barbital respectively. A similar reduction was seen with chloral hydrate but not with pentobarbital or methaqualon.

The "increased wakefulness" by modafinil is not only documented in mice but also in rats, monkeys, and cats. In rats, locomotor hyperactivity appeared at intraperitoneal doses equal to or greater than 32mg/kg. Over a period of 12 hours, locomotion in monkeys increased after a single dose from 68% (16mg/kg) to 880% when modafinil was given orally (64mg/kg). The percentage of wakefulness was also altered by modafinil in this species. At the single oral dose of 3, 6, and 12mg/kg, modafinil increased the wakefulness time by 21%, 160%, and 298% respectively. In the cat at the oral dose of 5mg/kg, modafinil increased the wakefulness and delayed the appearance of the slow wave and REM sleep phases.

In non-clinical models, equal wakefulness-promoting doses of methylphenidate and amphetamine increase neuronal activation throughout the brain, whereas modafinil, unlike classical psychomotor stimulants, predominantly affects brain regions implicated in regulating arousal, sleep, wake and vigilance.

Mechanism of Action

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

Modafinil-induced wakefulness can be attenuated by the α_1-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. Modafinil is not a direct-acting dopamine receptor agonist. However, in vitro and in vivo data indicate that modafinil binds to the dopamine transporter and inhibits dopamine reuptake. 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). The wake-promoting effects of modafinil are antagonized by D1 and D2 receptor antagonists, suggesting that dopaminergic receptors are necessary for its activity. In addition, alpha-methyl-p-tyrosine, a dopamine synthesis inhibitor, blocks the action of dopamine, but does not block locomotor activity induced by modafinil.

Another set of experiments suggests that modafinil may act on neuronal GABAergic function by increasing the turnover rate of 5-HT and by enhancing the activity of 5-HT_2 receptors. This hypothesis is supported by two sets of experiments. One shows that the acute and chronic treatment with modafinil increases significantly the levels of 5-hydroxyindolacetic acid (5-HIAA) the metabolite of 5-HT in the striatum of rats. The second set shows that modafinil inhibits the in vivo cerebral outflow of gamma aminobutyric acid (GABA) in guinea pigs and this inhibition is abolished by the pre-treatment of the animals with

ketanserine, a specific 5-HT2 antagonist but not by prazosin. Hence, α-1 receptors do not appear to be involved in the inhibitory release effect of modafinil on the GABAergic function.

The following findings add to the understanding of the mechanism of action of modafinil. Prazosin reduces the level of locomotion induced by modafinil in mice but not the increased locomotion by amphetamine and methylphenidate. In the mouse, amphetamine (4mg/kg IP) and methylphenidate (18mg/kg IP) potentiated the locomotor activity of norepinephrine given intra-ventricularly in the brain, while modafinil antagonized it. Unlike amphetamine (1-8mg/kg), modafinil at doses between 16mg and 128mg/kg IP did not cause stereotypies nor did it potentiate amphetamine-induced stereotypies in the same two species. The dose to obtain an LD_{50} was 6 times greater for amphetamine and 8 times greater for methylphenidate in isolated mice than in grouped mice; the dose for the LD_{50} of modafinil is only 1.6 times greater in isolated mice than in grouped mice. Finally, voltametric studies conducted in mice established a net difference between modafinil and amphetamine and methylphenidate. The amplitude of the oxidation peak of catecholamines recorded in the nigro-striatum remained unaffected by doses of modafinil in the range of 16 to 256mg/kg IP. Amphetamine at 2mg and 4mg/kg IP decreased the amplitude of this peak, while methylphenidate at 32 and 62mg/kg IP augmented greatly this peak.

Modafinil has weak to negligible interactions with receptors involved in the regulation of sleep/wake states (e.g., norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, orexin, and benzodiazepines). Modafinil also does not inhibit the activities of adenylyl cyclase, catechol-O-methyltransferase, glutamic acid decarboxylation, MAO-A or B, nitric oxide synthetase, tyrosine hydroxylase, or phosphodiesterases II-VI. Modafinil does not appear to be a direct α_1-adrenoreceptor agonist. However, modafinil binds to the norepinephrine transporter and inhibits norepinephrine uptake, but these interactions are weaker than those observed with the dopamine transporter.

In addition to its wake-promoting effects and ability to increase locomotor activity in animals, 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.

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

General Pharmacology

Apart from its central nervous system stimulating properties, modafinil exhibits very few other significant pharmacological effects. In genetically hypertensive rats, or in conscious or anaesthetized dogs, modafinil at intraduodenal doses of between 100 to 200mg/kg induced practically no effect on the cardiovascular and respiratory systems. Modafinil reduced moderately the induced hypertensive effect by amines such as epinephrine, tyramine, but essentially left intact the induced hypotensive effect by agents such as acetylcholine,

histamine, and angiotensin in anaesthetized dogs. After single doses of between 100 and 200mg/kg orally, modafinil did not alter urinary excretion, biliary secretion, pancreatic secretion, or peristaltic waves in dogs and rats. Finally, modafinil in Swiss mice had a stimulating effect on T cells at 1mg/kg, a slight stimulating effect on humoral immunity but no effect on cellular immunity.

Drug Interaction

Modafinil at oral doses between 20 and 100mg/kg did not modify: the predictive effects of the antidepressant activity of clomipramine and desipramine in mice the predictive effect of neuroleptic activity of chlorpromazine and haloperidol in rats; blood coagulation induced by warfarin (0.05 and 0.1mg/kg) in the Sprague-Dawley Rat; or the hypotensive effect of prazosin in genetically hypertensive rats.

TOXICOLOGY

Acute Toxicology

Acute toxicity studies were conducted with modafinil in the mouse, rat and dog. At high doses, all three species displayed hyperlocomotion and stereotypy movements. In mice and rats, mortality was delayed between Day 1 and Day 9. The following symptoms were observed in dogs at single doses of 200mg/kg and 400mg/kg: tachycardia, tachypnea, hyperthermia, moderate mydriosis during the stimulation phase, and delayed vomiting.

Species	*Route*	*Sex*	*$LD_{50} \pm SD$, mg/kg At 2 weeks*	*95% confidence Limits mg/kg*
Mouse	**PO**	**M + F**	**1,370 ± 93**	**1,208 - 1,562**
	IP	**M + F**	**792 ± 61**	**682 - 919**
Rat	**PO**	**M**	**2,000 ± 330**	**1,504 - 2,660**
		F	**1,600 ± 222**	**1,270 - 2,016**
	IP	**M**	**1,400 ± 179**	**1,102 - 1,778**
		F	**2,300 ± 293**	**1,811 - 2,921**

In the Beagle dog the oral lethal dose was between 300 and 400mg/kg.

Long-Term Toxicology

The toxicity of modafinil was initially evaluated in rats for a period of up to 3 months. After daily oral administration for 3 months of 50mg/kg, modafinil was relatively well tolerated. A slight anemia was observed, with hemosiderosis of the spleen, and a moderate increase of blood cholesterol. At higher doses, hepatomegalia without histological consequences appeared (100mg/kg) as well as an increase in the weight of kidneys and spleen (200mg/kg). The phenomena observed were reversible or in the process of reversibility two weeks after treatment discontinuation.

The toxicity of modafinil given orally was further evaluated in a 26-week study in rats. At the end of 26 weeks at the maximum dose of 200mg/kg the main change was an increase in liver weight (+18%) in males which appears to be due to enzymatic induction. Cholesterol levels, and the weight of the kidney and of the spleen were slightly increased in males.

The toxicity of modafinil was also examined via the oral route in Beagle dogs for twelve weeks at doses of 20, 50 and 75mg/kg/day. At the dose of 20mg/kg increase in serum cholesterol and alkaline phosphatase levels were seen. These changes were not associated with any histological alteration of the liver or of the other organs. At doses of 50 and 75mg/kg/day the same effects were present with a decrease in appetite and a weight loss. Although the increase was not statistically significant, weight of the liver, adrenals, and thyroid glands were increased. Enzymatic induction may explain the increased liver weight; and stress may have caused the increased adrenal weight. The histological examination did not detect any systematic treatment-related abnormality.

A 52-week study in the treated Beagle dog was also conducted with an oral dose of 10 to 40mg/kg/day. Animals receiving 20 or 40mg/kg/day had a significant increase in the weight of their liver and kidneys when compared to controls. No morphological changes were seen to account for the weight changes in the liver and kidneys at autopsy.

Carcinogenesis and Mutagenesis

The potential carcinogenicity of modafinil was tested in mice for 78 weeks and in rats for 104 weeks at an oral daily dose of 6, 30, and 60mg/kg/day. The highest dose studied is 0.75 to 1.5 (mouse) or 1.5 to 3 (rat) times greater than the recommended adult human daily dose of modafinil (200 to 400mg) on a mg/m^2 basis. At 60mg/kg/day (mouse) modafinil induced an increase in liver weight in line with a hepatocellular hypertrophy. Modafinil did not show carcinogenic potential nor did it cause an increase in spontaneously occurring tumors. The 60mg/kg/day (rat) male group had a statistically higher mortality rate than control groups. The mortality was associated with a higher incidence of moderate and chronic severe nephropathies which were probably treatment-related. The most severe renal lesions correlated also with significant higher levels of serum calcium, urea and cholesterol. There were no treatment-related changes in the 6mg/kg/day. The result of this study showed no evidence of any treatment-related disturbance of the normally expected spontaneous tumor profile of the Sprague-Dawley rat.

However, since the mouse study used an inadequate high dose that was not representative of a maximum tolerated dose, a subsequent carcinogenicity study was conducted in the Tg.AC transgenic mouse. Doses evaluated in the Tg.AC assay were 125, 250 and 500mg/kg/day, administered dermally. There was no evidence of tumorigenicity associated with modafinil administration; however, this dermal model may not adequately assess the carcinogenic potential of an orally administered drug.

Modafinil demonstrated no evidence of mutagenic or clastogenic potential in a series of in vitro (i.e., bacterial reverse mutation assay, mouse lymphoma tk assay, chromosomal aberration assay in human lymphocytes cell transformation assay in BALB/3T3 mouse embryo cells) assays in the absence or presence of metabolic activation, or in vivo (mouse bone marrow micronucleus) assays. Modafinil was also negative in the unscheduled DNA synthesis assay in rat hepatocytes.

Reproduction & Teratology

Fertility and General Reproduction Capacity

Oral administration of modafinil (doses of up to 480mg/kg/day) to male and female rats prior to and throughout mating, and continuing in females through Day 7 of gestation produced an increase in the time to mate at the highest dose; no effects were observed on other fertility or reproductive parameters. The no-effect dose of 240mg/kg/day was associated with a plasma modafinil exposure (AUC) approximately equal to that in humans at the dose of 200mg.

Assessment of Embryotoxicity

In studies conducted in rats and rabbits, development toxicity was observed at clinically relevant exposures. Embryotoxicity was observed in the absence of maternal toxicity when rats received oral modafinil (50, 100, or 200mg/kg/day) throughout the period of organogenesis. At a dose of 200mg/kg/day (5 times the maximum recommended daily human dose of 400mg on a mg/m^2 basis) there was an increase in resorption, hydronephrosis and skeletal variations. The higher no-effect dose for rat embryofetal developmental toxicity was associated with a plasma modafinil exposure approximately 0.25 to 0.5 times the AUC in humans at the recommended daily dose (RHD) of 200 to 400mg. However, in a subsequent study of up to 480mg/kg/day (plasma modafinil exposure approximately 1-2 times the AUC in humans at the RHD) no adverse effects on embryofetal development were observed.

Modafinil administered orally to pregnant rabbits throughout the period of organogenesis at doses of 45, 90, and 180mg/kg/day increased the incidences of fetal structural alterations and embryofetal death at the highest dose. The highest no-effect dose for developmental toxicity was associated with a plasma modafinil AUC approximately equal to the AUC in humans at the RHD.

Oral administration of armodafinil (the R-enantiomer of modafinil - not marketed in Canada; 60, 200, or 600mg/kg/day) to pregnant rats throughout the period of organogenesis resulted in increased incidences of fetal visceral and skeletal variations at the intermediate dose or greater and decreased fetal body weights at the highest dose. The no-effect dose for rat embryofetal developmental toxicity was associated with a plasma armodafinil exposure (AUC) approximately one-tenth times the AUC for armodafinil in humans treated with modafinil at the RHD. Modafinil administration to rats throughout gestation and lactation at oral doses of up to 200mg/kg/day resulted in decreased viability in the offspring at doses greater than

20mg/kg/day (plasma modafinil AUC approximately 0.05 to 0.1 times the AUC in humans at the RHD). No effects on postnatal developmental and neurobehavioral parameters were observed in surviving offspring.

Perinatal and Postnatal Toxicity Study

At oral doses of 20, 50 and 100mg/kg/day in the rat, modafinil induced no perinatal or postnatal toxicity.

Dependence Liability

Several animal models with rats and monkeys were used to evaluate the dependence liability of modafinil. In the discrimination model, cocaine-trained rats could not differentiate between 3 to 100mg/kg of modafinil and saline. It was only at the maximum tested dose of 250mg/kg that modafinil could substitute for cocaine. In this test, modafinil is approximately 250 times less potent than amphetamine and about 15 times less potent than *1*-ephedrine. In a second discriminate test, in which rats were trained to discriminate amphetamine from vehicle, modafinil showed no ability to produce an amphetamine-like effect except at a toxic dose of 250mg/kg. In another test, 91% of rats took an average of 35 sessions to acquire the discrimination of 1mg/kg of amphetamine (1mg/kg). By contrast, after an average of 69 sessions only 41% of the animals could discriminate modafinil at the dose of 64mg/kg. With the conditioned place preference test in rats, amphetamine 2mg/kg induced a clear cut place preference while modafinil at doses between 16 to 128mg/kg failed to do so. In an intravenous self-administration paradigm conducted with rats, modafinil (0.1 to 0.6mg/injection) did not act as a positive reinforcer when compared to cocaine (0.275mg/injection). Finally, in the self-administration test conducted in cocaine-trained monkeys, intravenous infusion of low dose (0.03mg/kg/injection) modafinil was not a substitute for cocaine. At a higher infusion dose of modafinil (0.1 and 0.3mg/kg/injection), the number of self-administrations increased above the number of administrations with the vehicle with a total average modafinil dose ranging from 0.4 to 34.7mg/kg per 1-hour session. When compared to *l*-ephedrine in the same experimental model, modafinil appear to be at least 3 times less potent than *l*-ephedrine.

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PART III: CONSUMER INFORMATION

[Pr]ALERTEC® *
(modafinil tablets)

This leaflet is part III of a three-part "Product Monograph" published when ALERTEC was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ALERTEC. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What is the most important information I should know about ALERTEC?

ALERTEC may cause you to have a serious rash or a serious allergic reaction. Stop ALERTEC and call your doctor right away or get emergency treatment if you have any of the following:

- skin rash, hives, sores in your mouth, or your skin blisters and peels
- swelling of your face, eyes, lips, tongue or throat
- trouble swallowing or breathing
- hoarse voice.

ALERTEC is not approved for use in children.

What the medication is used for:
ALERTEC is intended to relieve the excessive sleepiness due to medical conditions called narcolepsy (uncontrollable, brief episodes of sleep), obstructive sleep apnea (OSA) (breathing disorder during sleep) and circadian rhythm sleep disorder, shift work type (shift work disorder) (SWD). In narcolepsy, ALERTEC has no effect on cataplexy (sudden loss of muscular tone). In OSA, ALERTEC should be used along with successful standard medical treatments for the breathing disorder. In SWD, ALERTEC is intended to reduce your sleepiness but may not improve your work performance.

What it does:
As with many medicines affecting the brain, the mechanism of action of this medicine is not entirely known.

When it should not be used:
You should not take this medicine if you are already agitated or have severe anxiety.

You should not take this medication if you are allergic to modafinil, armodafinil (similar active ingredient in a product sold in the U.S.) or to any of the nonmedicinal ingredients in it or components of the container (see the paragraphs entitled ″What the medicinal ingredient is″ and ″What the important nonmedicinal ingredients are″ below).

The safety and efficacy of ALERTEC in children under the age of 18 has not been established and therefore it should not be used in pediatric patients.

What the medicinal ingredient is:
Modafinil

What the important nonmedicinal ingredients are:
Lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, sodium croscarmellose

What dosage forms it comes in:
Each tablet contains 100mg of an active ingredient called modafinil.

WARNINGS AND PRECAUTIONS

Serious skin rashes have been reported in patients using ALERTEC. (See "What is the most important information I should know about ALERTEC?")

BEFORE you use ALERTEC talk to your doctor or pharmacist if:

- you are using a hormonal birth control method. Women who use hormonal contraceptives such as birth control pills, shots, implants, intrauterine devices (IUDs), or patches, may have a higher chance for getting pregnant while taking ALERTEC, and for one month after stopping ALERTEC. Talk to your doctor about birth control methods that are right for you while using ALERTEC.
- you have high blood pressure, you have heart problems, or have had a heart attack.
- you have liver or kidney problems.
- you have or had a mental problem.
- you have abused medicines called "stimulants" or street drugs.
- you are pregnant, breast feeding or planning to become pregnant. There is very limited information on the safety of ALERTEC in these conditions. Therefore, ALERTEC is not recommended during pregnancy and breast feeding.
- you are taking other medicines, including prescription and non-prescription medicines, vitamins and herbal supplements. ALERTEC and many other medicines can interact with each other causing side effects. ALERTEC may affect the way other medicines work, and other medicines may affect how ALERTEC works. Keep a list of all the medicines you take. Your doctor will decide if you can take ALERTEC with your other medicines.

Special concerns:

Your doctor may request an electrocardiogram (ECG) before starting you on ALERTEC. You may also have your blood pressure and heart rate monitored while you are taking ALERTEC.

ALERTEC should not be used for the treatment of normal fatigue states. ALERTEC does not take the place of getting enough sleep.

There is no evidence that normal levels of attention can be

increased by ALERTEC.

ALERTEC may help treat the excessive sleepiness in most narcoleptic, OSA and SWD patients, but it may not stop all your sleepiness. Discuss your level of sleepiness with your doctor at each visit.

You should avoid driving a car, operating hazardous machinery or engage in any other potentially dangerous activity until you are certain of how ALERTEC affects your sleepiness.

Avoid drinking alcohol.

It may be critical that you continue to take your previously prescribed treatments (e.g., patients with breathing disorder during sleep must also receive a standard medical treatment for the breathing disorder while taking ALERTEC). ALERTEC is not a replacement for your CPAP machine. It is important that you continue to use your CPAP machine while sleeping.

Some effects of ALERTEC on the brain are similar to, but less than, other medications called "stimulants" that may be associated with the potential for abuse or misuse.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ALERTEC include: antipyrine, clomipramine, cyclosporine, dextroamphetamine, diazepam, methylphenidate, monoamine oxidase (MAO) inhibitors, oral contraceptives, phenytoin, propanolol, selective serotonin reuptake inhibitors, S-mephenytoin, triazolam, tricyclic antidepressant, warfarin.

ALERTEC and many other medicines, including prescription and non-prescription medicines, dietary supplements, and herbal remedies, can interact with each other causing side effects. ALERTEC may affect the way other medicines work, and other medicines may affect how ALERTEC works. Keep a list of all the medicines you take. Your doctor will decide if you can take ALERTEC with your other medicines.

PROPER USE OF THIS MEDICATION

Usual dose:
Take as directed by your doctor.

Patients with narcolepsy usually take ALERTEC as one (1) to two (2) tablets in the morning and one (1) to two (2) tablets at noon. Your doctor will try to adjust the dose to coincide with the periods of greatest sleepiness during the day. The second dose should normally be taken at noon or early in the afternoon to prevent difficulties falling asleep at bedtime. ALERTEC starts to work slowly. It may take an hour or so before you feel the effects.

It is not recommended to take more than 4 tablets a day (400mg). Do not take more tablets or take more often than you are told.

Patients with OSA usually take ALERTEC as two (2) tablets in the morning.

Patients with SWD usually take ALERTEC as two (2) tablets about 1 hour before their work shift.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. Make sure you take your medicine with you to show the doctor.

An overdose can cause insomnia, restlessness, disorientation, confusion, agitation, anxiety, excitation, hallucination, nausea, vomiting, diarrhea, an increase or decrease in heart rate, an increase in blood pressure and chest pain and can be fatal either alone or in combination with other drugs.

Missed Dose:
If you forget to take your medication, take it when you remember, unless it is close to the time for the next dose. Taking your medication in the evening or the late afternoon may prevent you from falling asleep at your usual bedtime, and should, therefore, be avoided.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects reported with this medicine are:

- Headache
- Difficulty falling asleep
- Nervousness
- Nausea
- Stuffy nose
- Diarrhea
- Back pain
- Anxiety
- Upset stomach
- Dizziness
- Somnolence
- Hypertension
- Tachycardia and/or palpitations (fast and/or abnormal heart beat)

These side effects tend to disappear after a few days or after a reduction of the dosage. Reaching the maximum daily dosage progressively over several days may prevent these side effects.

ALERTEC may cause serious side effects. Call your doctor or get emergency help if you experience any of the following infrequent side effects:

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek immediate medical emergency assistance
		Only if severe	In all cases	
Uncommon	Heart problems including chest pain			√
	Mental problems including depression, anxiety, hallucinations, mania, thoughts of suicide, aggression			√
	Serious skin rash			√
	Allergic reaction			√

This is not a complete list of side effects. For any unexpected effects while taking ALERTEC, contact your doctor or pharmacist.

HOW TO STORE IT

This medicine should be stored at room temperatures between 15° and 30°C. If the medication has expired (the expiry date appears on the label of the prescription and/or the treatment pack) throw away your tablets.

Keep these tablets in a safe place, out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at

http://www.tevacanadainnovation.ca

or by contacting the sponsor, Teva Canada Innovation, at:

1-855-223-6838

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