PrALERTEC®*

Modafinil
Tablets 100 mg
Central Nervous System Stimulant

Guide for Prescribers

ALERTEC® is manufactured by:
Teva Canada Limited
Toronto, Ontario M1B 2K9

ALERTEC® is distributed by:
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Montréal, Quebec H2Z 1S8

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This guide is part of the risk management measures included in the ALERTEC® Risk Management Plan and is designed to assure that healthcare professionals are:

- Aware of the product's safety profile and pertinent information on proper patient care;
- Aware of the importance of reporting adverse events in a compliant and detailed manner;
- Aware of the proper channels for reporting any suspected adverse reactions associated with the use of ALERTEC®.

INDICATIONS[1]

ALERTEC® (modafinil) is indicated for:

- The symptomatic treatment of excessive sleepiness in adult patients with narcolepsy.
- The symptomatic treatment of excessive sleepiness in adult patients with obstructive sleep apnea (OSA).
  - In OSA, ALERTEC® is indicated as an adjunct to successful standard treatment(s) for the underlying obstruction, when excessive sleepiness persists.
- The symptomatic treatment of excessive sleepiness in adult patients with circadian rhythm sleep disorder, shift work type (shift work disorder) (SWD).
  - In SWD, ALERTEC® is indicated for the symptomatic treatment of excessive sleepiness (as confirmed by multiple sleep latency test) associated with loss of a normal sleep-wake pattern (as confirmed by polysomnography).

Excessive Sleepiness

Sleep and wakefulness are regulated primarily by an interaction between sleep homeostatic and circadian processes.[2]

Excessive sleepiness is a frequent complaint of patients with:[3]

- **Obstructive sleep apnea**
  - Estimated prevalence of obstructive sleep apnea: 3% to 7% among adult males and 2% to 5% among adult females[4]
- **Narcolepsy**
  - Estimated prevalence of narcolepsy in the general population: 0.025% to 0.05%.[5,6]
- **Circadian rhythm sleep disorder, shift work type (shift work disorder)**
  - Estimate prevalence in night workers: 3.6% to 4.4%[7]

Prescribing Guide

Before you prescribe ALERTEC®, please review the following information closely:

- Proper Patient Selection
- Dosing & Administration – Dosing Considerations
- Important Safety Information
- Medical Information & Reporting Instructions

Proper Patient Selection

- ALERTEC® is a central nervous system stimulant 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.
- In SWD, ALERTEC® is indicated for the symptomatic treatment of excessive sleepiness (as confirmed by multiple sleep latency test) 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.
- 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.
- There is no evidence that normal levels of alertness can be heightened by ALERTEC®.
- 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.

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and effectiveness in pediatric patients have not been established. Therefore, ALERTEC® is not approved for use in pediatric patients for any indication including Attention Deficit Hyperactivity Disorder (ADHD).

Geriatrics (>65 years old): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

Contraindications

- ALERTEC® is contraindicated in 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 also contraindicated in patients in agitated states and in patients with severe anxiety.
- ALERTEC® is contraindicated in women who are pregnant or may become pregnant due to the potential risk to the fetus.

  Women should be advised regarding the use of effective contraception during treatment as modafinil may reduce effectiveness of steroidal contraceptives.

Pediatrics (<18 years of age)

- Safety and effectiveness in pediatric patients have not been established. ALERTEC® is not approved for use in pediatric patients for any indication including Attention Deficit Hyperactivity Disorder (ADHD). Serious cutaneous adverse reactions have been reported with modafinil use in pediatric patients.

Before Initiating Therapy

- A cardiac evaluation, including an electrocardiogram (ECG), should be obtained for all patients before treatment with ALERTEC® is initiated. This is particularly recommended for patients with coronary artery disease, a recent history of myocardial infarction, or unstable angina. Patients with abnormal findings should receive further evaluation before ALERTEC® treatment is considered.
- Women of reproductive potential should have a negative pregnancy test within a week prior to starting treatment with modafinil.
- The effectiveness of steroidal contraceptives may be reduced due to induction of CYP3A4/5 by modafinil. Alternative or concomitant methods of contraception other than steroidal are recommended for patients treated with ALERTEC®, and for two months after discontinuation of ALERTEC®.

Dosage & Administration – Dosing Considerations

Pediatrics (<18 years of age)

- The safety and efficacy of modafinil in children under the age of 18 years have not been established. Therefore, modafinil is not indicated for use in pediatric patients.

Geriatrics

- In geriatric 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.

Severe Hepatic Impairment

- In patients with severe hepatic impairment, the dosage of ALERTEC® should be reduced to one-half of the usual recommended dose.

Concomitant use with CYP3A4 substrates

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

Concomitant use with CYP2C19 substrates

- Because modafinil and its metabolite, modafinil sulfone, are reversible inhibitors of the drug-metabolizing enzyme CYP2C19, co-administration of modafinil with drugs which are largely eliminated via that pathway may increase the circulating levels of those compounds, which may have prolonged elimination upon co-administration with ALERTEC® and may require dosage reduction and monitoring for toxicity.

Recommended Dose and Dose Adjustment

Please consult the ALERTEC® Product Monograph for details on recommended dose and dose adjustment.

Important Safety Information – Warnings and Precautions

The following safety information should be considered before prescribing ALERTEC®. Please consult the ALERTEC® Product Monograph for further details on the information provided below:

General

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.

Normal Fatigue States

- ALERTEC® should not be used for the treatment of normal fatigue states.

Use in Combination with Other CNS 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.

Patients Using Cyclosporine

- Blood levels of cyclosporine may be reduced when used with ALERTEC®. Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustment for cyclosporine should be considered.

Alcohol Consumption

- Patients should be advised to avoid alcohol consumption while taking ALERTEC®.

Cardiovascular

- **All patients should undergo a cardiac evaluation, including an electrocardiogram (ECG), prior to ALERTEC® initiation. This is particularly recommended for patients with coronary artery disease, a recent history of myocardial infarction, or unstable angina.**
- 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 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 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.
- 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 300 mg and after total daily doses of more than 400 mg.
- **Risk of stroke:** Three epidemiological studies with a common design were conducted in administrative databases assessing the cardiovascular risk of modafinil. One of the 3 studies, with a sample size best suited for detecting an effect, suggested an increase in the incidence rate of stroke in modafinil-treated patients compared to patients not treated with modafinil. Overall, a causal relationship between modafinil and stroke has not been established.

Dependence/Tolerance

- The potential for abuse should be considered when prescribing ALERTEC®. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (e.g., methylphenidate, amphetamine, or cocaine) abuse or a history of psychiatric disorders. Patients should be observed for signs of misuse (e.g., incrementation of doses or drug-seeking behavior).

Withdrawal

- The effects of withdrawal were monitored following 9 weeks of ALERTEC® 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.

Driving and Operating Machinery

- Patients should be alerted to exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

- ALERTEC® may cause induction of hepatic microsomal enzymes, especially at doses greater than 400 mg. The metabolism of oral anticoagulants, antidepressants, 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.

Immune

Angioedema and Anaphylactoid Reactions

- Angioedema and anaphylactic reactions 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 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.
- If a multi-organ hypersensitivity reaction is suspected, ALERTEC® should be discontinued.

Neurologic

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

Psychiatric

- Psychiatric adverse experiences, including psychotic episodes, have been reported in patients treated with ALERTEC®. Post-marketing adverse events associated with the use of modafinil have included mania, delusions, hallucinations, suicidal ideation and aggression, some resulting in hospitalization. Many, but not all patients, had a prior psychiatric history.
- 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®.
- A history of psychiatric disorders may also increase the risk of abuse or misuse of ALERTEC®.

Renal

Severe Renal Impairment

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

Reproductive Health: Female and Male Potential

Women of childbearing potential / Contraception

- ALERTEC® is contraindicated in women who are pregnant or may become pregnant. Therefore, before initiation of treatment in women of childbearing potential, a negative pregnancy test must be available. Women of reproductive potential should be advised to use effective contraception during therapy with modafinil and for two months after discontinuation of ALERTEC® treatment.

Teratogenic Risk

- Based on human data, ALERTEC® is potentially teratogenic.

Lactation

- ALERTEC® is not recommended during lactation.

Skin

Severe Cutaneous Adverse Reactions

- Rare cases of serious or life-threatening rash, including SJS, Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) – requiring hospitalization and discontinuation of treatment – have been reported in association with the use of modafinil in adults and children in worldwide post-marketing experience.
- There are no factors that are known to predict the risk of occurrence, or the severity of rash associated with modafinil.
- 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.

Adverse 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
- back pain
- nausea
- anxiety
- rhinitis
- dizziness
- nervousness
- dyspepsia
- diarrhea
- insomnia

Medical Information & Reporting Instructions

For healthcare professionals with specific questions about ALERTEC®, please contact us at:

MedInfo
Medical Affairs
Teva Canada Innovation
1080 Beaver Hall Hill, Suite 1200
Montreal (Quebec) H2Z 1S8
Call toll-free at 1-855-223-6838
Email: TCIMedical.Affairs@tevapharm.com

You can report any suspected adverse reactions associated with the use of ALERTEC® to:

- **Teva Canada Limited** at 1-866-530-6065 Fax: 1-416-335-4472; or.
- **Health Canada** by:
  - Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax;
  - Calling toll-free at 1-866-234-2345

If you want more information about ALERTEC®:

- Please consult the product monograph for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this guide.
- Find the full Product Monograph that is prepared for healthcare professionals by visiting the Health Canada website (https://pdf.hres.ca/dpd_pm/00071543.PDF), the manufacturer's website (http://www.tevacanada.com), or by calling 1-855-223-6838.

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