Pr ALERTEC®*

Modafinil

Tablets 100 mg

Central Nervous System Stimulant

Guide for Prescribers

This material was developed by Teva Canada Innovation, as part of the risk minimization plan for ALERTEC®. This material is not intended for promotional use.

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

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

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®.

1. INDICATIONS

ALERTEC® 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® 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).

2. EXCESSIVE SLEEPINESS

Excessive sleepiness is a frequent complaint of patients with:[2]

- Obstructive sleep apnea
  - Estimated prevalence of obstructive sleep apnea: 4% men/2% for women
- Narcolepsy
  - Estimated prevalence of narcolepsy in the general population: 0.03% to 0.16%
- **Circadian rhythm sleep disorder, shift work type (shift work disorder)**
  - Estimate prevalence in night workers: 2-5%

Sleep and wakefulness are regulated primarily by an interaction between sleep homeostatic and circadian processes.[3]

3. PRESCRIBING GUIDE

Before you prescribe ALERTEC®, please review the information in each of the following sections:

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

3.1. 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.

ALERTEC® is indicated for the symptomatic treatment of excessive sleepiness (as confirmed by multiple sleep latency tests) 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 ALERTEC® 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.

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

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. Females of reproductive potential should have a negative pregnancy test within a week prior to starting treatment with modafinil.

Pregnant women should be advised of the potential risk to a fetus. Women should be advised regarding the use of effective contraception during treatment as ALERTEC® may reduce effectiveness of steroidal contraceptives.

3.2. Dosing & Administration

3.2.1. Dosing Considerations

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

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.

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

3.2.2. Recommended Dose and Dose Adjustment

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

3.3. Important Safety Information

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

3.3.1. 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.

- 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.

3.3.2. Angioedema and Anaphylactic Reactions

- 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).

3.3.3. 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.

3.3.4. Persistent Sleepiness

- Patients with abnormal levels of sleepiness who take ALERTEC® should be advised that their level of wakefulness may not return to normal.

3.3.5. Psychiatric Symptoms

- 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
- Many, but not all, patients had a prior psychiatric history.
- If psychiatric symptoms develop in association with ALERTEC® administration, consider discontinuing ALERTEC®.

3.3.6. Normal Fatigue States

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

3.3.7. Occupational Hazards

- There is evidence that, because of possible over-stimulation and overconfidence, ALERTEC® alters the ability to perform hazardous activities in some patients.

3.3.8. CPAP Use in Patients with OSA

- In OSA, ALERTEC® is indicated as an adjunct to successful standard treatment(s) for the underlying obstruction. If ALERTEC® is used adjunctively with continuous positive airway pressure (CPAP), the encouragement of, and periodic assessment of, CPAP compliance is necessary.
- If 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®.

3.3.9. 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. 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%).
- Cardiovascular adverse reactions increase significantly after single doses of 300 mg and after total daily doses of more than 400 mg.

3.3.10. 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.

3.3.11. Patients Using Steroidal Contraceptives

- The effectiveness of steroidal contraceptives may be reduced when used with ALERTEC® and for two months after discontinuation of therapy. Alternative or concomitant methods of contraception other than steroidal are recommended for patients treated with ALERTEC®, and for two months after discontinuation of ALERTEC®.

3.3.12. Patients Using Cyclosporine

- The 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 when these drugs are used concomitantly.

3.3.13. Potential for Abuse

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 abuse. 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.

ALERTEC® may cause induction of hepatic microsomal enzymes, especially at doses greater than 400 mg. The metabolism of oral anticoagulants, antidepressant, anticonvulsants, and oral contraceptives may be increased.

ALERTEC® should be administered at a reduced dose in patients with severe hepatic impairment.

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

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

ALERTEC® is contraindicated during pregnancy.

ALERTEC® is not recommended during lactation.

3.3.14. 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

3.4. 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 1-800-268-4127 option 3
Email: TCIMedical.Affairs@tevapharm.com

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

- **Teva Canada Limited** at 1-800-268-4127 option 3 (English), 1-877-777-9117 (French), Telefax: 1-416-335-4472; or
- **Health Canada** by:
  - Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax;
  - Calling toll-free at 1-866-234-2345

This document, as well as the full product monograph, can be found at the following web address: https://www.tevacanada.com/globalassets/canada-ph2/pdf-documents-en/specialty-pdfs/0619_tci_alertec_pm_en.pdf

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. The product monograph is also available by calling 1-855-223-6838.

3.5. References

1. Teva Canada Limited. ALERTEC® Product Monograph. June 5, 2019. Available at: http://tevacanadainnovation.ca/downloads/Alertec_PM_EN.pdf

2. American Academy of Sleep Medicine. International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual. Westchester, IL: American Academy of Sleep Medicine; 2001.

3. Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci. 1995;15:3526–3538.

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