



## CDEC FINAL RECOMMENDATION

### ZOLPIDEM TARTRATE (Sublinox – Meda Valeant Pharma Canada) Indication: Insomnia

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that sublingual zolpidem tartrate not be listed.

#### **Reason for the Recommendation:**

There is insufficient evidence to determine if sublingual zolpidem provides comparable clinical benefit versus other hypnotics available in Canada for the treatment of acute, short-term insomnia.

#### **Background:**

Sublingual zolpidem is indicated for the short-term treatment and symptomatic relief of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. The product monograph states that treatment with sublingual zolpidem should usually not exceed seven to 10 consecutive days, and that the use of hypnotics should be restricted for insomnia where disturbed sleep results in impaired daytime functioning. Zolpidem is available in 5 mg and 10 mg sublingual orally disintegrating tablets. The recommended dose for adults is 10 mg once daily immediately before bedtime.

#### **Summary of CDEC Considerations:**

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of sublingual zolpidem, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients. There were no randomized controlled trials (RCTs) that met the minimum inclusion criteria for the CDR systematic review. Specifically, no RCTs using the 5 mg or 10 mg tablet were identified comparing sublingual zolpidem with zopiclone, benzodiazepines, or placebo for the approved Health Canada indication. CDEC therefore considered a summary of information relevant to sublingual zolpidem, prepared by CDR, which included:

- trials of sublingual zolpidem that did not meet the CDR systematic review protocol
- a trial of oral zolpidem versus zopiclone
- pharmacokinetic data
- systematic reviews of pharmacotherapies for insomnia
- additional harms data

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### **Patient Input Information**

The following is a summary of key information provided by one patient group that responded to the CDR call for patient input:

- People with insomnia indicated that they suffer from fatigue, headaches, inability to think clearly, depression, anxiety, and stress. They noted that their inability to sleep can affect their ability to work, participate in social or family activities, and can leave them feeling disagreeable or irritable and lacking sexual desire or drive.
- Many people who suffer from insomnia have done so for a long time, sometimes several decades. Many have tried a variety of different medicines, which usually have proven to be inadequate and which often have been associated with undesirable side-effects.
- People with insomnia stated that they would be interested in sublingual zolpidem if it could improve their sleep and, more importantly, if they did not have to worry about being drowsy the next day or becoming dependent on the medication.

### **Summary of Findings:**

There were no RCTs that met the inclusion criteria for the CDR systematic review. Comparative efficacy data using the sublingual formulation were limited to a single double-blind RCT comparing 10 mg sublingual zolpidem against 10 mg oral zolpidem (Ambien) in acute insomnia patients (N = 73). Study OX22-006 was a double-blind, double-dummy, two-period crossover RCT. This study did not meet the inclusion criteria for the CDR systematic review because, although oral zolpidem has received a Notice of Compliance for the treatment of acute, short-term insomnia, it has never been marketed in Canada.

Study OX22-006 demonstrated the following:

- Sublingual zolpidem was superior to oral zolpidem for latency to persistent sleep, with a mean difference (MD) of -10.3 minutes (95% confidence interval [CI]: -4.3 to -16.2).
- Sublingual zolpidem was superior to oral zolpidem for sleep onset latency; MD of -8.6 minutes (95% CI: -3.0 to -14.0).
- There was a modest increase in total sleep time with sublingual zolpidem compared with oral zolpidem; MD of 7.22 minutes (95% CI: 0.02 to 14.43).
- There was no statistically significant difference in wake after sleep onset; MD of 1.13 minutes (95% CI: -5.03 to 7.28).
- At least one adverse event was reported for 15.7% of patients treated with sublingual zolpidem and 22.9% of patients treated with oral zolpidem.

### **Cost and Cost-Effectiveness**

The manufacturer submitted a cost minimization analysis comparing sublingual zolpidem with oral zopiclone for the short-term management of primary insomnia, based on the submitted price of \$██████ per tablet, or \$██████ per day. The manufacturer reported that sublingual zolpidem, at a cost of \$██████ per 10-day treatment, would result in additional costs between \$██████ and \$██████ per 10-day treatment compared to branded zopiclone (Imovane). There was no comparison between sublingual zolpidem and generic zopiclone, which is considerably less expensive (\$2.23 to \$4.68 per 10-day treatment). In addition, the manufacturer did not consider benzodiazepines (flurazepam, nitrazepam, temazepam, and triazolam) that are indicated for the short-term treatment of insomnia and reimbursed under public drug plans in Canada, which are also less expensive than sublingual zolpidem (\$0.36 to \$2.50 per 10-day

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treatment). At the submitted price of \$ [REDACTED] per tablet, sublingual zolpidem is more expensive than other therapies that are reimbursed for the short-term management of primary insomnia.

### Other Discussion Points:

CDEC noted the following:

- At the submitted price, 10 mg of sublingual zolpidem is considerably more costly than 5 mg and 7.5 mg of generic zopiclone.

### Research Gaps:

CDEC noted that there is an absence of evidence regarding the following:

- Though there are several published RCTs available for oral zolpidem, there were no studies comparing sublingual zolpidem against treatments for insomnia that are marketed in Canada (e.g., zopiclone or short-acting benzodiazepines).

### CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

### Regrets:

**July 17, 2013:** None

**September 18, 2013:** One CDEC member could not attend the meeting.

### Conflicts of Interest:

None

### About this Document:

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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