CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-997

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 24, 2009
To:	Russell Katz, MD, Director Division of Neurology Products
Through:	Claudia Karwoski, PharmD, Director (Acting) **Division of Risk Management** Jodi Duckhorn, MA, Team Leader **Patient Labeling and Education Team** **Division of Risk Management**
From:	Nancy Carothers, RN, BA Patient Product Information Reviewer **Patient Labeling and Education Team** **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide), and Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Edluar (zolpidem tartrate sublingual tablets) 5mg, 10mg
Application Type/Number:	NDA 21-997
Applicant/sponsor:	Orexo AB, Sweden
OSE RCM #:	2008-1567

1 INTRODUCTION

This review is written in response to a request from the Division of Neurology Products for the Division of Risk Management's Patient Labeling and Education Team to review the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) for Edluar (zolpidem tartrate sublingual tablets), which includes the draft Medication Guide (MG) and a Timetable for Submission of Assessments of the effectiveness of the REMS.

FDA has determined that Edluar poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Edluar. FDA has determined that Edluar meets all three criteria for a Medication Guide as set forth in 21 CFR 208.1. Edluar is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use Edluar. FDA has also determined that Edluar is a product for which patient labeling could help prevent serious adverse events, and patient adherence to the directions for use is crucial to the drug's effectiveness.

2 MATERIAL REVIEWED

- DRAFT Edluar (zolpidem tartrate sublingual tablets) PI submitted by the Sponsor on June 13, 2008.
- DRAFT Edluar (zolpidem tartrate sublingual tablets) MG submitted by the Sponsor on June 13, 2008.
- DRAFT Edluar (zolpidem tartrate sublingual tablets) container labeling submitted by the Sponsor on December 16, 2008.
- DRAFT Edluar (zolpidem tartrate sublingual tablets) blister pack labeling submitted by the Sponsor on December 16, 2008 and February 20, 2009.
- DRAFT Edluar (zolpidem tartrate sublingual tablets) Proposed REMS submitted by the sponsor on January 12, 2009.

3 BACKGROUND

The sponsor submitted the New Drug Application (NDA 21-997) for zolpidem tartrate sublingual tablets on January 12, 2006 and this resulted in a Refuse to File. The sponsor resubmitted the NDA on May 14, 2008. This NDA is submitted pursuant to Paragraph 505(b)(2); AMBIEN is the reference listed drug (RLD). At the time of the original submission, the sponsor stated that they would submit an updated label, based on an AMBIEN label that had been approved on May 7, 2008. On June 13, 2008 the sponsor submitted a revised draft of the Edluar (zolpidem tartrate sublingual tablets) labeling which referenced the approved AMBIEN labeling.

The draft MG follows the class labeling for sedative-hypnotics and includes the serious and significant public health concerns of sleep driving and other complex behavioral changes related to the use of this product.

The determination that a MG is necessary was based on the fact that Edluar (zolpidem tartrate sublingual tablets) belongs to a class of drugs (sedative- hypnotics) that meet the three criteria for a REMS and Medication Guide.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to provide FDA with new authorities to require sponsors of approved drugs to develop and comply with section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

On January 12, 2009 the sponsor submitted the Proposed Risk Evaluation and Mitigation Strategy (REMS) which includes a Timetable for Submission of Assessments.

The proposed tradename for zolpidem tartrate sublingual tablets is Edluar. This name was found to be acceptable by the Division of Medication Error, Prevention, and Analysis.[1]

4 DISCUSSION

4.1 MEDICATION GUIDE

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy. In our review of the MG, we have:

- ensured that the MG is consistent with the class language for other sedative-hypnotics,
- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- removed unnecessary or redundant information,
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20,
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.
We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4.2 PROPOSED REMS

a. Goal

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[1] M. Griffis. Proprietary Name Review – Edluar (Zolpidem Tartrate Sublingual Tablets) 5mg, 10mg, dated February 12, 2009.

The Sponsor has proposed the following REMS goal:

b(4)

The primary purpose for requiring a REMS is to communicate the serious risks associated with Edluar (zolpidem) through use of a Medication Guide. We suggest revising the goal slightly to:

The goal of the REMS is to inform patients of the serious risks associated with the use of Edluar (zolpidem tartrate sublingual tablets), and how to use Edluar (zolpidem tartrate sublingual tablets) correctly to help prevent serious adverse events.

b. REMS Elements

- Medication Guide – The MG and Instructions for Use will be dispensed with each Edluar prescription. As described in REMS, the sublingual tablets will be provided in unit-of-use packaging and requires no repackaging by the pharmacy.
- The Timetable for Submission of Assessments is as follows:
  - 1st assessment: 18 months after approval
  - 2nd assessment: 3 years after approval
  - 3rd assessment: 7 years after approval

4.3 CARTON AND CONTAINER

The sponsor must comply with 21 CFR 208.24(d) by including a statement, alerting pharmacists to dispense the MG with the product on the carton and containers for all strengths and quantities.

- The statement on all of the cartons says.

b(4)

- This statement is not in compliance with 21 CFR 208.24 (d) and is not acceptable. We propose the following language.

  "Dispense the enclosed Medication Guide to each patient."

4.2 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the sponsor's proposed REMS and Medication Guide for Edular (zolpidem tartrate sublingual tablets) meets the statutory requirements outlined in section 505-1 of FDAAA and in 21 CFR 208. We have the following comments and recommendations:

We have the following comments on the proposed REMS:

1. We recommend the REMS goal be revised as follows:

   The goal of the REMS is to inform patients of the serious risks associated with the use of Edluar (zolpidem tartrate sublingual tablets), and how to use Edluar (zolpidem

tartrate sublingual tablets) correctly to help prevent serious adverse events.

2. See the appended Edluar REMS proposal (Appendix A) for additional track changes corresponding to comments in this review.

3. The statements on the carton and container to satisfy the requirements under 21 CFR 208.24(d) are not acceptable. We recommend the following language dependent upon whether the Medication Guide accompanies that product or is enclosed in the carton e.g., unit-of-use.

> "Dispense the enclosed Medication Guide to each patient." or
> "Dispense the accompanying Medication Guide to each patient."

4. We recommend including in the approval letter a reminder of the sponsor's responsibility to provide the information needed (methodology) to assess the effectiveness of the REMS as stated above, including an evaluation of:

- Patients' understanding of the serious risks of Edluar (zolpidem tartrate sublingual tablets).
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

5. The sponsor should submit for review a detailed plan to evaluate the patients' understanding about the safe use of Edluar at least 2 months before they plan to conduct the evaluation. The submission should include:

    - All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Edluar. This should include, but not be limited to:
        - Sample size and confidence associated with that sample size
        - How the sample will be determined (selection criteria)
        - The expected number of patients to be surveyed
        - How the participants will be recruited
        - How and how often the surveys will be administered
        - Explain controls used to minimize bias
        - Explain controls used to compensate for the limitations associated with the methodology
    - The survey instruments (questionnaires and/or moderator's guide).
    - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

We have the following comments on the proposed Medication Guide:

6. The instruction for taking the Edluar sublingual tablet appears in the first section, "What is the most important information I should know about Edluar?" It says, "Place the tablet under the tongue, where it will rapidly disintegrate. Do not swallow or take with water." We moved this instruction to the section, "How should I take Edluar?" because this type of instruction does not appear in the first section in the referenced AMBIEN

MG. However, we defer to the RD as to whether the change in the formulation, from an oral to a sublingual tablet, warrants placement of this information in the "What is the most important information I should know..?" section of the MG.

7. In the section, "What is Edluar?":

b(4)

8. In the section, "How should I take Edluar?":

- We suggest using the term "faster" to be consistent with the class language an b(4)
- bullets in this section that describe when to take Edluar, how to remove the tablet from the packaging, and how to take the tablet sublingually are not consistent with the class language but we suggest including this information to ensure the safe and effective use of this new formulation.
- bullet says that the tablet disintegrates. The term was deleted b(4)

9. In the section, "What are the possible side effects of Edluar?":

- we deleted the statement, to be consistent with the class language. "Depersonalization" is used in the PI. See 5.3. We question whether this concept would be clearly understood by patients using this product. We suggest including this "side effect" under Patient Counseling so that it can be explained by the patient's physician. b(4)
- we deleted the statements to be consistent with the class language. Also, the specific information regarding the problem when using Edluar is not in the PI. The PI and MG must be consistent.
- some of the common side effects used in the class language are different from the common side effects listed in this MG. Two of these are "diarrhea" and "drugged feeling," and we added these to this MG because they are in the Edluar PI. Diarrhea occurs at a higher rate compared to the study subjects receiving placebo. Other additional side effects "drugged feeling," fatigue, and headache have been included because they are listed in the PI as among the most commonly observed side effects for this medicine. c See Tables 1 and 2 under 6.1.
- the information has been deleted b(4) to be consistent with the class language. We suggest that this information would be appropriate in the Patient Counseling section of the PI since it involves consultation with the patient's physician.
- the last 5 withdrawal symptoms listed under the topic, "After you stop taking a sleep medicine" b(4)

were deleted to be consistent with the class language. See the AMBIEN MG. b(4)

10. In the section, "How should I store Edluar?" we included the statement, "Protect from light and moisture." because it appears in the PI. However, it is not in the class language for sedative-hypnotics.

Please let us know if you have any questions.

10 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Risk Assessment / Risk Mitigation-*_____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nancy B Carothers
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DRUG SAFETY OFFICE REVIEWER