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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

21-476

Trade Name: Lunesta 1-, 2, and 3-mg Tablets

Generic Name(s): (eszopiclone)

Sponsor: Sepracor, Inc.

Agent:

Approval Date: December 15, 2004

Indication: Provides for use in the treatment of insomina

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-476

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-476

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-476

Sepracor Inc.
Attention: Cynthia L Kirk, Ph.D.
Vice President, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Dr. Kirk:

Please refer to your new drug application (NDA) dated January 20, 2003, received January 31, 2003, submitted under section 505(b)of the Federal Food, Drug, and Cosmetic Act for Lunesta (eszopiclone) 1mg, 2mg, and 3mg tablets.

We acknowledge receipt of your additional submissions dated:

March 12, 2003	June 13, 2003	October 16, 2003	March 5, 2004	September 30, 2004
March 17, 2003	June 18, 2003	November 11, 2003	March 9, 2004	November 8, 2004
March 18, 2003	June 24, 2003	November 25, 2003	April 1, 2004	November 9, 2004
March 19, 2003	June 30, 2003	December 16, 2003	May 20, 2004	November 19, 2004
March 24, 2003	July 8, 2003	December 18, 2003	June 14, 2004	November 22, 2004
March 25, 2003	July 15, 2003	December 22, 2003	August 11, 2004	November 24, 2004
April 15, 2003	July 25, 2003	February 6, 2004	August 20, 2004	
May 29, 2003	August 28, 2003	February 11, 2004	August 26, 2004	
June 5, 2003	October 14, 2003	March 2, 2004	September 29, 2004	

Your June 14, 2004 submission constituted a complete response to our February 27, 2004 action letter.

This new drug application provides for the use of Lunesta (eszopiclone) Tablets in the treatment of insomnia.

Labeling
We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). With regard to immediate container and carton labels, we note that the labels submitted November 24, 2004 do not accurately reflect your tradename "Lunesta." Therefore, please submit corrected FPL as agreed to in a December 14, 2004 telephone conversation between Dr. Renmeet Gujral of the Division and yourself. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15

of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-476.**" Approval of this submission by FDA is not required before the labeling is used.

Pediatric Research Equity Act (PREA)
All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 to less than 3 years and deferring pediatric studies for ages 3 to 17 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of insomnia in pediatric patients ages 3 to 17 years.

Final Report Submission: March 2010

Submit the final study report to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated '**Required Pediatric Study Commitments**".

Chem(b)(4)nufacturing and Controls
1. A (b)(4) re-test date for eszopiclone drug substance is granted.
2. A 24 month expiry is granted for the 2 mg and 3 mg strength tablets in (b)(4) bottles and (b)(4) blisters.
3. A 15 month expiry is granted for the 1 mg light blue tablet in (b)(4) bottles.

Methods Validation
We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Promotional Materials
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MedWatch

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Renmeet Gujral, Pharm.D., Regulatory Project Manager, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Temple
12/15/04 06:17:24 PM

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-476

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-476

Sepracor Inc.
Mohammed A. Salem, Ph.D., RAC
Director, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Dr. Salem:

Please refer to your new drug application (NDA) dated January 30, 2003, received January 31, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ESTORRA™ (eszopiclone) Tablets 2 mg and 3 mg.

We also refer to our Chemistry Review Discipline letter dated October 1, 2003, providing preliminary notice of Chemistry, Manufacturing, and Controls deficiencies in this application.

We acknowledge receipt of your submissions dated:

March 12, 2003	March 17, 2003	March 18, 2003	March 19, 2003
March 24, 2003	March 25, 2003	April 15, 2003	May 29, 2003
June 13, 2003	June 18, 2003	June 30, 2003	July 8, 2003
July 15, 2003	August 28, 2003	October 1, 2003	October 14, 2003
October 16, 2003	November 11, 2003	November 25, 2003	November 28, 2003
December 16, 2003	December 22, 2003	February 6, 2004	February 11, 2004

We also acknowledge receipt of your submissions dated February 6, 2004 and February 11, 2004. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

Clinical

- Please clarify the actual numbers of reports of neoplasm in study 190-049. There appears to be a disproportionate number of reports of adverse events of neoplasia in the eszopiclone group in this long-term double blind study of eszopiclone in patients with chronic insomnia. Depending on the tables we consult there are somewhere between 16 and 24 reports of neoplasia in the 593 eszopiclone treated patients and 0/195 reports in the placebo group. We recognize from the verbatim terms that many of these reports may have been improperly coded; however, in the absence of the patient data or a clearer explanation, we

cannot make that assumption. Though we are interested in an explanation of all of these cases, we are particularly curious about three cases:

a. Subject 0450024- by your description, this patient seems to be progressing steadily in a work up for disseminated cancer and then appears lost to follow-up after she drops out of the study. This case was not reported as a serious adverse event even though the reason for her discontinuation is coded as "neoplasia".

b. Subject 0406001- dropped out of the study for an adverse event coded as Breast Neoplasm. The summary reports that she experienced a "lump" in her left breast after approximately 1½ months of double-blind treatment. It was considered benign, presumably based on ultrasound and mammography that were conducted, but the results were not described. The subsequent course of her breast lump over time was not described yet study drug was discontinued upon discovery of the lump.

c. Subject 0421004- a 62 year old female with no medical problems at screening who reported a "nodule in throat" after approximately 5 months of double-blind treatment. This nodule was described as resolving 10 days after cessation of treatment. The narrative provides no other information and she appears lost to follow-up.

Once all of the cases have been adequately examined, comparative incidence rates for the occurrence of neoplasia need to be calculated. Of the potential comparisons that you may make on the occurrence rates for neoplasia, one should be based on patient-years exposure to drug or placebo. If patients were lost to follow-up before a definitive diagnosis of the problem was made, then these cases should be counted as neoplasia in at least one analysis. It will also be important to examine the timing of the observations of neoplasia, as the plausibility of such an event as drug-related could be affected (e.g., a finding at 2-4 weeks would not be plausibly drug-related but one at 6 months might be).

We can not say that these cases represent a persuasive signal of drug-induced neoplasia, but the numerical imbalance of the reports of neoplasia and case histories that these numbers represent need to be thoroughly examined prior to considering eszopiclone for approval, especially given the pre-clinical findings of mammary and lung tumors with zopiclone and the finding of clastogenicity of eszopiclone and S-desmethyl-zopiclone.

- It appears that there is an increased incidence of both "Infection" and "accidental injury" on drug compared to placebo, but you have not adequately examined these issues.

Specifically, we note that there are a number of events that could reasonably be considered as "Infection" that you have not included under this term (for example, pharyngitis, bronchitis, etc.). In addition, you need to examine all cases and classify appropriately; viral syndromes are not necessarily the same as an abscess. Please re-examine your database and identify all possible verbatim terms that could reasonably be considered to represent an

infection, and perform appropriate analyses of the comparative incidences of these events. Similarly, please examine your database for all possible verbatim terms that could reasonably be considered to represent accidental injury (for example, laceration, bruising, etc.) and perform the appropriate comparative analyses.

- We note a very high (and dose related) incidence of unpleasant taste in the controlled trials, and are concerned that this might have partially unmasked the trial. Please address this concern. For example, you might consider analyzing results separately in the patients who did, or did not, report this adverse event. You may also wish to examine the time course of this event; if the event occurred only early in the course of treatment, it might have had a negligible effect on the outcome later in time. You may also consider the potential effects of unblinding on the various endpoints used in the trials.

- We have determined that Estorra should be placed in Category IV of the Controlled Substances Act.

- You will need to develop a 1 mg tablet strength, or alternatively develop a scored 2 mg strength. The 1 mg dose was clearly effective (for sleep latency) in elderly patients, and should also be used in severely hepatically impaired patients, whose exposure is twice that of normal patients. We believe that it would be important to have available the 1 mg dosage strength for these and other sensitive patients.

- You have not provided sufficient data on orthostatic vital sign changes. We believe these data are important, and request that you provide this information, adequately assessed and evaluated at appropriate times (e.g., at least at Tmax) after dosing.

  Further, you have not provided an adequate presentation of the proportion of patients who meet appropriate outlier (potentially clinically significant) criteria for vital signs and EKG intervals at appropriate times after dosing. Please do so.

Labeling

- In labeling you suggest that there is little reason for concern about next day psychomotor impairment or memory problems — after zopiclone is taken, but it was not clear on what objective time-course data this reassurance was based and further explanation is needed. This explanation should describe studies that objectively explored the effects on cognition and psychomotor function at relevant time points after study drug was taken. These descriptions should focus on what functions were measured and whether or not a difference in performance was detected. You should comment on objective measures of memory impairment and sedative/psychomotor effects. Reassuring statements about the lack of effect on psychomotor function and cognition based on spontaneous reports or subjective measures alone are of little help in determining when or if impairment is no longer present.

You should also note that in the presence of a measured impairment on the DSST and in the absence of formal studies of driving ability one can not make any conclusions on how the next day residual effect may influence a complicated function such as driving. Please also note that an objectively measured decrement in functioning together with a reported feeling of being rested and alert (as you suggest is the case) is not reassuring from the standpoint of driving safety, but is cause for concern.

- Please explore the effects of eszopiclone discontinuation and any potential loss of therapeutic effect compared to placebo in the 6-month datasets. Ideally this type of comparison is made in patients who, after taking drug for 6-months, are re-randomized to take either placebo or continue on drug. Since, to our knowledge, this was not done in your development program a comparison of the loss of treatment effect of eszopiclone treated patients when switched to placebo versus placebo patients who continued on placebo during the treatment withdrawal phase of the study would be acceptable.

  We note in your draft labeling that you describe the effects of zopiclone withdrawal on the incidence of rebound insomnia. Rebound insomnia is defined as insomnia that is worse than that experienced at baseline. However, there are often measurable losses of effect that are significantly different from placebo that do not reach the level of "rebound". In addition to an analysis of classical rebound, we are also interested in an analysis of this latter phenomenon. Results of this type of exploration should be discussed under the heading of Withdrawal Emergent Anxiety and Insomnia; or

- Please review and respond to our bracketed comments in the draft labeling that we have attached to this action letter.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Safety Update

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

- Describe in detail any significant changes or findings in the safety profile.

- When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

  a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  b. Present tabulations of the new safety data combined with the original NDA data.

c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

- Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

- Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

- Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

- Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

- Provide English translations of current approved foreign labeling not previously submitted.

Biopharmaceutics

- We request the adoption of the following dissolution method and specification for the 2 mg and 3 mg strengths of eszopiclone tablets.

Summary of Drug Product Dissolution Method and Specification	
Dosage Form	eszopiclone tablets
Strengths	2.0 and 3.0 mg
Apparatus	USP Type 2 apparatus (paddle)
Media	—
Volume	—
Speed of Rotation	— rpm
Acceptance Criterion	Q= — at 30 minutes

Chemistry, Manufacturing, and Controls

Your submission of February 6, 2004, responds to our Chemistry Review Discipline letter of October 1, 2003. We will review that submission during the next review cycle. For completeness sake, those requests are repeated below:

1. The DMF holders for (RS)-zopiclone have been sent deficiency letters.

2. Provide a representative Certificate of Analysis for each — used in the manufacture of eszopiclone.

3. Provide information on the commercial batch size for eszopiclone drug substance and clarify if the (RS)-zopiclone batches are mixed for manufacture of eszopiclone drug substance. Provide a detailed description of the procedure used to qualify a supplier of (RS)-zopiclone.

4. Provide a representative certificate of analysis (COA) for — and the plan for qualification of a — supplier. In addition, assay and impurity specifications should be added as acceptance criteria for —

5. The specifications for (RS)-zopiclone should include related substances (as individual specified, individual unspecified and total impurities), and — Provide the validated method with GC and HPLC chromatograms used to detect impurities and — - - for (RS)-zopiclone. Demonstrate that the validated methods detect the impurities/ — from each DMF supplier of (RS)-zopiclone.

6. Provide exact values of — or the reference standard since the LOD and LOQ are much lower than — (refer to page 557, Vol. 1.2). The exact values of all — should also be reported for each batch. In addition, include — esting in the reference standard.

7. For eszopiclone drug substance specifications:
   a) State the exact appearance of eszopiclone such as "powder" or "crystalline powder" instead of referring to eszopiclone as a solid.
   b) The term "Single Largest Unknown" in impurities should be changed to "Individual Unspecified".
   c) At least a — specification for — is recommended in terms of the percent of —
   d) Provide justification of the microbial specifications (t — — even though the release and stability data show the value to be —

8. Provide chromatograms of eszopiclone from each (RS)-zopiclone supplier utilizing impurity method — Also identify the unmarked impurity in chromatogram (page 106, Vol. 1.1).

9. Provide batch analysis data for eszopiclone drug substance batches manufactured using (RS)-zopiclone from — and show that the eszopiclone manufactured from the different (RS)-zopiclone sources is equivalent.

10. Eszopiclone drug substance stability specifications for (R)-zopiclone and related substances should be tightened to the release specifications or as outlined in ICH Q3B(R) since the stability data showed no increases over time.

11. Impurities — are not measured at release since the impurity method — s not specific for these impurities. Include a validated method for testing and a specification for — at release and on stability and provide release data for all the drug substance batches and data for those placed on stability.

12. Provide information on the drug substance batch evaluated for — studies and clarify if the batch was manufactured using the commercial manufacturing process at a commercial site.

13. Provide exact amounts of each impurity observed during the — studies of eszopiclone drug substance (refer to information provided on pages 558-559, Vol. 1.2).

14. Provide the stability protocol and commitment for testing future stability batches of (S)-zopiclone drug substance.

15. Provide justification for the — proposed for — in the Estorra Tablets 2 and 3 mg batch compositions (page 6, Vol. 1.3).

16. Define the term "appropriate BSE/TSE certification" for magnesium stearate. Also include the BSE/TSE certification from the supplier as per FDA guidelines.

17. Provide a list of the equipment (class and sub-class) used to manufacture Estorra tablets.

18. Clarify whether the eszopiclone drug substance batches from — are mixed in the manufacture of a drug product batch.

19. Clarify the following statement under drug product in-process controls: "During commercial production, results outside of the proposed ranges may result in equipment adjustment."

20. Provide the sampling plan for the production batch analyses. The sampling plan should include details on the number of samples selected for analysis per batch and the location of the sample selected (e.g. beginning, middle, end).

21. The impurity method — for drug product does not include impurities — — Include a validated method for testing and a specification for — at release and on stability including future stability protocols. Provide data for all the drug product batches and for those placed on stability. Also, impurity — is not identified on the chromatograms provided for impurity method — In addition, provide information on the source and certificate of analysis (COA) on each of the impurity reference standards.

22. The term "Single Largest Unknown" should be changed to "Individual Unspecified" impurity in the drug product specifications.

23. The proposed drug product qualification limit for — should be tightened to NMT — (as recommended by ICH Q3B(R), or provide data to support that — has been qualified to the — .

24. Provide justification for the microbial specifications (— —) for the drug product even though the release and stability data show the value to be —

25. Provide details on the bulk drug product packaging system.

26. Samples of — should be provided at the time of methods validation package.

27. For the description section of package insert, the contents of Estorra tablets should be listed — The following is recommended: "Eszopiclone is formulated as film-coated tablets for oral administration. Each ESTORRA tablet contains either 2 or 3 mg eszopiclone. —

28. The container and carton labels for the drug product should contain —

Nomenclature

The Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the proprietary name, Estorra, because of its look-alike similarity to Estrace®, a drug product that already exists in the marketplace. The two products share the same first three letters, E, S, and T, which contributes to the look-alike similarity between the two product names. In addition, when written in cursive, the latter portion of each name, 'orra' of Estorra and 'ace' of Estrace, can look similar. Moreover, the letter 'a' of Estorra may look like the letter 'e' of Estrace if the writing is trailed off. Estorra and Estrace share several overlapping product characteristics. Both products are available as 2 mg tablets and may have similar dosing intervals (daily vs bedtime). The prescribers and patient populations may also overlap. Estorra and Estrace are both marketed in bottles of 100 tablets and may be stored near each other in a dispensing area. The quantity dispensed for both products could also overlap (e.g., 30 tablets). Prescriptions for several Estrace indications of use have a starting dose of 1 mg to 2 mg per day. Estorra 2 mg is the starting dose for the geriatric population. Thus, a prescription for Estrace 2 mg HS could be misinterpreted as Estorra 2 mg HS. Based on these similarities, there is a high potential for name confusion between the two product names.

Pediatric Research Equity Act (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Our decision on whether to grant the waiver or to defer these studies will be conveyed to you in a separate letter.

Jurisdiction

As communicated to you earlier, Agency responsibility for review of this NDA will be transferred to the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) after the issuance of this action letter. Therefore, future submissions to this NDA should be forwarded to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and
Addiction Drug Products (HFD-170)
Attention: Division Document Room, Rm. 8B45
5600 Fishers Lane
Rockville, Maryland 20857

In regard to other communications, please check with Ms. Parinda Jani, Chief Project Management Staff (HFD-170), at (301) 827-7422 for specifics on the appropriate contact person in that division. As explained in the past, the Division of Neuropharmacological Drug Products (HFD-120) will consult with HFD-170 and will participate, when appropriate, in communications with your firm regarding this action letter and the product development of eszopiclone.

Advertising Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Letter of Intent and End of Review Conference

Within 10 days after the date of this letter, you are required to amend this application, notify the Agency of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Therefore, if you wish an end of review conference, as provided under 21 CFR 314.102(d), to discuss what steps need to be taken before the application may be approved, your request for an informal meeting or telephone conference should be directed to Ms. Parinda Jani, Chief Project Management Staff, at (301) 827-7422.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

130 pages redacted from this section of the approval package consisted of draft labeling