CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-476

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

13. Patent Information on Any Patent That Claims the Drug

This section provides patent information on the following patents covering Sepracor's NDA 21-476 for eszopiclone:

- U.S. Patent No. 6,319,926
- U.S. Patent No. 6,444,673

November 21, 2002

Central Document Room
Center for Drug Evaluation Research
FOOD AND DRUG ADMINISTRATION
12229 Wilkins Avenue
Rockville, MD 20852

RE: **NDA NUMBER 21-476, SEPRACOR INC.**
PATENT INFORMATION, U.S. PAT. NO. 6,319,926

Dear Sir/Madam:

This letter is submitted under 21 USC §355(b)(1) in connection with Sepracor's New Drug Application No. 21-476 for eszopiclone.

The following U.S. Patent is owned by Sepracor Inc.

U.S. Patent No. 6,319,926, expires 16 January 2012

The undersigned declares that U.S. Pat. No. 6,319,926 covers the method of use of eszopiclone. This product is the subject of this application for which approval is being sought.

A claim of patent infringement could reasonably be asserted with respect to this patent if a person not licensed by the owner engaged in the manufacture, use or sale of the drug for which applicant submitted the application.

Sepracor respectfully requests that, upon approval of the application, the above patent information be published in the "Prescription and OTC Drug Product Patent and Exclusivity Data" section of the U.S. Department of Health and Human Services publication *APPROVED DRUG PRODUCTS with Therapeutic Equivalence Evaluations.*

VERY TRULY YOURS,

Douglas E. Reedich
Sr. Vice President, Legal Affairs
& Chief Patent Counsel

Time Sensitive Patent Information Pursuant to 21 C.F.R. 314.53 for NDA 21-476

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ESTORRA™
Active Ingredient(s):	eszopiclone
Strength(s):	2.0 mg; 3.0 mg
Dosage Form:	tablet
Approval Date:	____________________

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: 6,319,926
Expiration Date: 16 January 2012

Type of Patent--Indicate all that apply:

Drug Substance (Active Ingredient) ___Y ___N
Drug Product (Composition/Formulation) ___Y ___N
Method of Use _√_ Y ___N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

treatment of insomnia

Name of Patent Owner: Sepracor Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

not applicable

B. The following declaration statement is required by 21CFR 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number 6,319,926 covers the composition, formulation and/or method of use of eszopiclone. This product is:

___ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.
OR
_√_ the subject of this application for which approval is being sought.

Signed: [signature]

Date: 21 Nov 02

November 21, 2002

Central Document Room
Center for Drug Evaluation Research
FOOD AND DRUG ADMINISTRATION
12229 Wilkins Avenue
Rockville, MD 20852

RE: **NDA NUMBER 21-476, SEPRACOR INC.**
PATENT INFORMATION, U.S. PAT. NO. 6,444,673

Dear Sir/Madam:

This letter is submitted under 21 USC §355(b)(1) in connection with Sepracor's New Drug Application No. 21-476 for eszopiclone.

The following U.S. Patent is owned by Sepracor Inc.

U.S. Patent No. 6,444,673, expires 16 January 2012

The undersigned declares that U.S. Pat. No. 6,444,673 covers the drug substance (active ingredient) eszopiclone and the drug product (composition/formulation) of eszopiclone. This product is the subject of this application for which approval is being sought.

A claim of patent infringement could reasonably be asserted with respect to this patent if a person not licensed by the owner engaged in the manufacture, use or sale of the drug for which applicant submitted the application.

Sepracor respectfully requests that, upon approval of the application, the above patent information be published in the "Prescription and OTC Drug Product Patent and Exclusivity Data" section of the U.S. Department of Health and Human Services publication *APPROVED DRUG PRODUCTS with Therapeutic Equivalence Evaluations.*

VERY TRULY YOURS,

Douglas E. Reedich
Sr. Vice President, Legal Affairs
& Chief Patent Counsel

Time Sensitive Patent Information Pursuant to 21 C.F.R. 314.53 for NDA 21-476

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ESTORRA™
Active Ingredient(s):	eszopiclone
Strength(s):	2.0 mg; 3.0 mg
Dosage Form:	tablet
Approval Date:	____________________

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: 6,444,673
Expiration Date: 16 January 2012

Type of Patent--Indicate all that apply:

Drug Substance (Active Ingredient) √_Y ___N
Drug Product (Composition/Formulation) √_Y ___N
Method of Use _ Y ___N

b. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

not applicable

Name of Patent Owner: Sepracor Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

not applicable

B. The following declaration statement is required by 21CFR 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number 6,444,673 covers the composition, formulation and/or method of use of eszopiclone. This product is:

___ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.
OR
_√_ the subject of this application for which approval is being sought.

Signed: [signature]

Date: 21 Nov 02

14. A Patent Certification with Respect to Any Patent That Claims the Drug

This section provides information related to patent certification and claimed exclusivity for NDA 21-476.

November 21, 2002

Central Document Room
Center for Drug Evaluation Research
FOOD AND DRUG ADMINISTRATION
12229 Wilkins Avenue
Rockville, MD 20852

RE: **NDA NUMBER 21-476, SEPRACOR INC.**
PATENT CERTIFICATION

Dear Sir/Madam:

This letter is submitted under 21 USC §355(b)(1) in connection with Sepracor's New Drug Application No. 21-476 for eszopiclone.

The subject original application is submitted under Section 505(b)(1) of the FD&C Act. Therefore patent certification pursuant to 21 CFR 314.50(i) is not applicable.

VERY TRULY YOURS,

Douglas E. Reedich
SR. Vice President, Legal Affairs
& Chief Patent Counsel

EXCLUSIVITY SUMMARY FOR NDA # 21-476 SUPPL #___

Trade Name Lunesta tablets

Generic Name eszopiclone

Applicant Name Sepracor Inc.

HFD # 120

Approval Date If Known December 15, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_x__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

___505(b)(1)___

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_x_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

__5 years_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_x__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____
NDA# _____ _____
NDA# _____ _____

2. Combination product. N/A

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_x_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations,

identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____

_____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /_ __/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature
Title:

Date 1/13/05

Renmeet Gujral, Pharm.D
Regulatory Project Manager

Signature of Office/
Division Director

Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products

Form OGD-011347 Revised 05/10/2004

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

/s/

Russell Katz
1/28/05 09:10:49 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-476 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: original: January 31, 2003 **Action Date:** December 15, 2004

HFD 120 **Trade and generic names/dosage form:** Lunesta (eszopiclone) 1mg, 2mg, 3mg tablets

Applicant: Sepracor Inc. **Therapeutic Class:** Sedative Hypnotic

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Insomnia

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply:** x **Partial Waiver** x **Deferred** ____ **Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age range being partially waived: yr. 0- 3

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- X **Too few children with disease to study**
- X **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age range being deferred: yr._3-17_

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- X **Too few children with disease to study**
- X **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): ___**March 2010**_____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Renmeet Gujral, Pharm.D.
Regulatory Project Manager

_____

Russell Katz, M.D.
Director, Division of Neurpharmacological Drug Products

cc: NDA 21-476
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

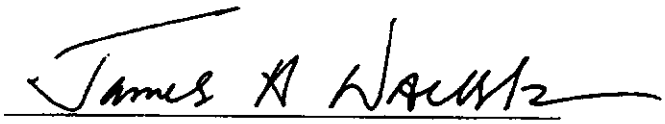
/s/

Russell Katz
1/28/05 04:39:34 PM

16. Debarment Certification

Sepracor Inc. hereby certifies that it did not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this New Drug Application for Estorra (eszopiclone) tablets.

All physician investigators and their staffs who participated in any phase of clinical research that supports this NDA have been confirmed to be in good standing. Likewise, we have confirmed that no employee of Sepracor Inc., or of any contract research organization involved in the development of Estorra™, has been debarred or at any time has been implicated in any criminal activity associated with the causes of debarment or been investigated in conjunction with any criminal activity associated with pharmaceutical research and development.



James Allen Wachholz
Executive Director, Regulatory Affairs

19. Financial Information

In accordance with 21 CFR, Part 54, all principal investigators and subinvestigators listed on the signed FDA Forms 1572 for Sepracor-sponsored clinical trials referenced in this NDA have submitted signed Financial Disclosure statements indicating the extent to which, if any, they received compensation from Sepracor in any of the four following categories:

Category 1. Financial arrangements whereby the value of the compensation could be influenced by the outcome of the clinical trial. This should include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product, such as a royalty interest.

Category 2. Significant payment of other sorts, excluding the costs of conducting the clinical trial or other clinical studies. This could include, for example, payments made to the investigator or the institution to support activities that have a monetary value greater than $25,000 (i.e., grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria).

Category 3. A proprietary or financial interest in the test product, such as patent, trademark, copyright, or licensing agreement.

Category 4. A significant equity interest in the sponsor of the clinical trial. This would include, for example, any ownership interest, stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or any equity interest in a publicly traded company exceeding $50,000.

The signed financial disclosures made by each of the investigators also certified whether any of the above categories of interest were held, and in what amount(s), by his or her spouse or dependent children. Lastly, as part of disclosure, the investigators agreed to contact Sepracor promptly if any of the above information changed during the course of the clinical trial or up to one year after completion.

The information listed below is provided on the following pages for 21 CFR 54 Financial Disclosure:

- Compliance Statement
- Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators

Compliance Statement

Compliance Statement for 21 CFR 54 Financial Disclosure: Form FDA 3454

Based on the signed financial disclosure forms collected for all principal investigators and subinvestigators who participated in clinical trials that support efficacy and/or safety claims for eszopiclone, Sepracor certifies that to the best of the company's knowledge, no investigators, spouses, or dependent children of investigators received compensation for Categories 1 and 3, or compensation beyond the acceptable limits for Categories 2 ($25,000) and 4 ($50,000).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Estorra™ (eszopiclone) tablets	
	IND 58,647	**See attached list of investigators**
	NDA 21-476	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Robert Scumaci	**Executive VP, Finance and Administration**
FIRM/ORGANIZATION: **Sepracor Inc.**	
SIGNATURE: *[signature]*	DATE: 1-14-03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (6/02)

Created by: PSC Media Arts (301) 443-2454 EF

19.1 Financial Disclosure Described by Study and Principal Investigator

Sepracor has financial disclosures on file for principal investigators and subinvestigators who participated in all complete and ongoing studies of ESTORRA™ (eszopiclone) submitted in support of the efficacy and safety label claims:

- Clinical Pharmacology Studies: 190-001, 190-002, 190-005, 190-010, 190-011, 190-012, 190-013, 190-014, 190-015, 190-016, 190-018, 190-019, 190-020, 190-021, 190-022, 190-023

- Controlled Clinical Studies: 190-024, 190-025, 190-026, 190-045, 190-046, 190-047, 190-048, 190-049

Table 19.1-1 lists all research sites by principal investigator who participated in these studies, along with the level of compensation disclosed for each of the four compensation categories previously described. None of the principal investigators or subinvestigators at any of the following research sites disclosed receiving any compensation in Categories 1 through 4.

For the principal investigators and subinvestigators participating in the above-mentioned studies that completed on or before 31 December 2000 (i.e., 190-001, 190-002, 190-005, 190-010, 190-012, 190-019, 190-021, and 190-026), updated financial disclosure information was requested. Updated financial disclosure information received to date is reflected in the table below. Per the updated information collected, there was no change in the financial disclosure information from the investigators' initial disclosure.

Table 19.1-1 Investigators and Financial Disclosure Information

Investigator Name	Study Number	Financial Categories – Amounts in U.S. $			
		1	2	3	4
Michael Alexander, M.D. Niagara Falls, Ontario, Canada	190-047	0	0	0	0
Nancy Abdou, M.D. Lenexa, Kansas	190-010 190-019 190-021 190-023	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0
Donald L. Anderson, M.D. Loma Linda, California	190-048 190-049	0 0	0 0	0 0	0 0
Luis Angles, M.D. Mission, Kansas	190-048 190-049	0 0	0 0	0 0	0 0
Mira Baron, M.D. Cleveland, Ohio	190-049	0	0	0	0
Danny Bartel, M.D. Wichita Falls, Texas	190-049	0	0	0	0
Louise M. Beckett, M.D. Oklahoma City, Oklahoma	190-049	0	0	0	0

Table 19.1-1 Investigators and Financial Disclosure Information

Investigator Name	Study Number	Financial Categories – Amounts in U.S. $			
		1	2	3	4
David Berwald, M.D. St. Louis, Missouri	190-049	0	0	0	0
Michael Biber, M.D. Newton, Massachusetts	190-046 190-047	0 0	0 0	0 0	0 0
Gregory Bishop, M.D. San Diego, California	190-049	0	0	0	0
Jed Black, M.D. Stanford, California	190-026	0	0	0	0
Marshall B. Block, M.D. Phoenix, Arizona	190-048 190-049	0 0	0 0	0 0	0 0
Gary Bloomgren, M.D. Tacoma, Washington	190-013	0	0	0	0
Richard Bogan, M.D., FCCP Columbia, South Carolina	190-046 190-047	0 0	0 0	0 0	0 0
Scott Bonvallet, M.D. Bellevue, Washington	190-049	0	0	0	0
Nancy G. Campbell, M.D. Houston, Texas	190-048 190-049	0 0	0 0	0 0	0 0
Jesse M. Carr, M.D. Glendale, California	190-046 190-047	0 0	0 0	0 0	0 0
Bruce Cleeremans, M.D. Irvine, California	190-047	0	0	0	0
Martin Cohn, M.D. Naples, Florida	190-012 190-046 190-047	0 0 0	0 0 0	0 0 0	0 0 0
Patricia Coleman, M.D. East Lansing, Michigan	190-049	0	0	0	0
Lydia G. Corn, M.D. Sarasota, Florida	190-049	0	0	0	0
Bruce Corser, M.D. Cincinnati, Ohio	190-024 190-025 190-026 190-045 190-046 190-047	0 0 0 0 0 0	0 0 0 0 0 0	0 0 0 0 0 0	0 0 0 0 0 0
Robert Dawkins, Ph.D., MPH Mobile, Alabama	190-046	0	0	0	0
Michael W. DePriest, M.D. Las Vegas, Nevada	190-049	0	0	0	0
Isabelle Desjardins, M.D. Clearwater, Florida	190-048 190-049	0 0	0 0	0 0	0 0
Seymour Diamond, M.D. Chicago, Illinois	190-049	0	0	0	0
Bhupesh Dihenia, M.D. Lubbock, Texas	190-046 190-047	0 0	0 0	0 0	0 0

Table 19.1-1 Investigators and Financial Disclosure Information

Investigator Name	Study Number	Financial Categories – Amounts in U.S. $			
		1	2	3	4
John Docherty, M.D.	190-048	0	0	0	0
White Plains, New York	190-049	0	0	0	0
Clyde Dos Santos, M.D.	190-046	0	0	0	0
Anaheim, California	190-047	0	0	0	0
Walter D. Dunbar, M.D.	190-049	0	0	0	0
Atlanta, Georgia					
Stephen Duntley, M.D.	190-047	0	0	0	0
St. Louis, Missouri					
Steven Eisen, M.D.	190-049	0	0	0	0
Philadelphia, Pennsylvania					
Helene Emsellem, M.D.	190-046	0	0	0	0
Chevy Chase, Maryland	190-047	0	0	0	0
Donald L. England, M.D.	190-048	0	0	0	0
Eugene, Oregon	190-049	0	0	0	0
Milton K. Erman, M.D.	190-026	0	0	0	0
La Jolla, California	190-045	0	0	0	0
	190-046	0	0	0	0
	190-047	0	0	0	0
	190-048	0	0	0	0
John Ervin, M.D.	190-049	0	0	0	0
Kansas City, Missouri					
Neil Feldman, M.D.	190-046	0	0	0	0
St. Petersburg, Florida	190-047	0	0	0	0
	190-048	0	0	0	0
Thomas Fiel, D.O.	190-049	0	0	0	0
Tempe, Arizona					
Patrick Finnegan, M.D.	190-049	0	0	0	0
Longmont, Colorado					
Jonathan Flescher, M.D.	190-046	0	0	0	0
Raleigh, North Carolina					
Raul E. Gaona, M.D.	190-049	0	0	0	0
San Antonio, Texas					
W. Thomas Garland, M.D.	190-049	0	0	0	0
Lawrenceville, New Jersey					
Suzanne Gazda, M.D.	190-049	0	0	0	0
San Antonio, Texas					
Harry I. Geisberg, M.D.	190-049	0	0	0	0
Anderson, South Carolina					
Jeffrey Geohas, M.D.	190-048	0	0	0	0
Chicago, Illinois	190-049	0	0	0	0
Edward Gillie, M.D.	190-048	0	0	0	0
Fort Myers, Florida	190-049	0	0	0	0
J. Christian Gillin, M.D.	190-046	0	0	0	0
San Diego, California	190-047	0	0	0	0

Table 19.1-1 Investigators and Financial Disclosure Information

Investigator Name	Study Number	Financial Categories – Amounts in U.S. $			
		1	2	3	4
Lawrence D. Ginsberg, M.D. Houston, Texas	190-049	0	0	0	0
David Greeley, M.D. Spokane, Washington	190-049	0	0	0	0
Randall Grimshaw, M.D. Austin, Texas	190-049	0	0	0	0
Paul B. Haberman, M.D. Santa Monica, California	190-047	0	0	0	0
John Harsh, Ph.D. Hattiesburg, Mississippi	190-046 190-047	0 0	0 0	0 0	0 0
Robert W. Hart, M.D. Elk Grove Village, Illinois	190-046 190-047	0 0	0 0	0 0	0 0
James Heaton, M.D. Blairsville, Georgia	190-048 190-049	0 0	0 0	0 0	0 0
Joseph Q. Henkle, M.D. Springfield, Illinois	190-046	0	0	0	0
James J. Herdegen, M.D. Chicago, Illinois	190-046	0	0	0	0
James R. Herron, M.D. Chicago, Illinois	190-048 190-049	0 0	0 0	0 0	0 0
Dennis Hill, M.D. Winston-Salem, North Carolina	190-046 190-047	0 0	0 0	0 0	0 0
Max Hirshkowitz, Ph.D. Houston, Texas	190-046	0	0	0	0
Peter Holland, M.D. Boca Raton, Florida	190-047	0	0	0	0
John Holmes, M.D. Mission, Kansas	190-046	0	0	0	0
E. Walter Hood, M.D. Atlanta, Georgia	190-048 190-049	0 0	0 0	0 0	0 0
Richard P. Hull, M.D. Huntsville, Alabama	190-048 190-049	0 0	0 0	0 0	0 0
Steven Hull, M.D. Overland Park, Kansas	190-047	0	0	0	0
Adrian Jaffer, M.D. La Jolla, California	190-049	0	0	0	0
Rakesh Jain, M.D. Lake Jackson, Texas	190-048 190-049	0 0	0 0	0 0	0 0
Andrew Jamieson, M.D. Dallas, Texas	190-026	0	0	0	0
Andrew Jamieson, M.D. Plano, Texas	190-045 190-046 190-047	0 0 0	0 0 0	0 0 0	0 0 0
Donald Jasinski, M.D. Baltimore, Maryland	190-016	0	0	0	0

Table 19.1-1 Investigators and Financial Disclosure Information

Investigator Name	Study Number	Financial Categories – Amounts in U.S. $			
		1	2	3	4
William P. Jennings, M.D. San Antonio, Texas	190-049	0	0	0	0
Shelly Kafka, M.D. Duncansville, Pennsylvania	190-048	0	0	0	0
Robert Kaufmann, M.D. Atlanta, Georgia	190-049	0	0	0	0
Christopher Kelsey, M.D. San Diego, California	190-049	0	0	0	0
Alan J. Kivitz, M.D. Duncansville, Pennsylvania	190-049	0	0	0	0
Keith Klatt, M.D. Portland, Oregon	190-049	0	0	0	0
Arthur R. Knodel, M.D. Tacoma, Washington	190-026	0	0	0	0
Jerrold Kram, M.D. Oakland, California	190-046 190-047	0 0	0 0	0 0	0 0
Andrew Krystal, M.D. Durham, North Carolina	190-046 190-047	0 0	0 0	0 0	0 0
Dennis Lawlor, M.D. Olathe, Kansas	190-047	0	0	0	0
Philip Leese, M.D. Lenexa, Kansas	190-001 190-005 190-015 190-020 190-022	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Michael T. Levy, M.D. Staten Island, New York	190-048 190-049	0 0	0 0	0 0	0 0
Benjamin Lewis, M.D. Ninety Six, South Carolina	190-049	0	0	0	0
J. Gila Lindsley, Ph.D. North Andover, Massachusetts	190-047	0	0	0	0
James Loftin, M.D. Dallas, Texas	190-046 190-047	0 0	0 0	0 0	0 0
Vijay Mahajan, M.D. Toledo, Ohio	190-047	0	0	0	0
Timothy G K Mant, M.D. London, United Kingdom	190-014	0	0	0	0
Thomas Marbury, M.D. Orlando, Florida	190-011 190-013 190-014	0 0 0	0 0 0	0 0 0	0 0 0
W. Vaughn McCall, M.D. Winston-Salem, North Carolina	190-046 190-047	0 0	0 0	0 0	0 0
Dennis McCluskey, M.D. Mogadore, Ohio	190-049	0	0	0	0

Table 19.1-1 Investigators and Financial Disclosure Information

Investigator Name	Study Number	Financial Categories – Amounts in U.S. $			
		1	2	3	4
William J. McEntee, M.D. Sarasota, Florida	190-048	0	0	0	0
Harris H. McIlwain, M.D. Tampa, Florida	190-048 190-049	0 0	0 0	0 0	0 0
Louis J. McNabb, M.D. Fullerton, California	190-046 190-047	0 0	0 0	0 0	0 0
Dennis Morrison, D.O. Springfield, Missouri	190-011	0	0	0	0
Adam Moscovitch, M.D. Calgary, Alberta, Canada	190-046 190-047	0 0	0 0	0 0	0 0
Nabil A. Moufarrej, M.D. Shreveport, Louisiana	190-046	0	0	0	0
William S. Mullican, M.D. Evansville, Indiana	190-049	0	0	0	0
Linda P. Murray, D.O. St. Petersburg, Florida	190-049	0	0	0	0
Robert Nett, M.D. San Antonio, Texas	190-048 190-049	0 0	0 0	0 0	0 0
Diane M. Normandin, M.D. Clearwater, Florida	190-049	0	0	0	0
Michael J. Noss, M.D. Cincinnati, Ohio	190-048 190-049	0 0	0 0	0 0	0 0
Robert Noveck, M.D., Ph.D. New Orleans, Louisiana	190-013	0	0	0	0
Margarita Nunez, M.D. St. Petersburg, Florida	190-048 190-049	0 0	0 0	0 0	0 0
Howard L. Offenberg, M.D. Gainesville, Florida	190-049	0	0	0	0
William Orr, Ph.D. Oklahoma City, Oklahoma	190-047	0	0	0	0
James F. Pagel, Jr., M.D. Pueblo, Colorado	190-046 190-047	0 0	0 0	0 0	0 0
Ralph Pascualy, M.D. 1 Seattle, Washington	190-046 190-047	0 0	0 0	0 0	0 0
Vernon Pegram, M.D. Birmingham, Alabama	190-047	0	0	0	0
Richard G. Pellegrino, M.D. Hot Springs, Arkansas	190-047 190-048 190-049	0 0 0	0 0 0	0 0 0	0 0 0
Ana Y. Perez, M.D. San Antonio, Texas	190-049	0	0	0	0
A. Thomas Perkins, M.D., Ph.D. Raleigh, North Carolina	190-046	0	0	0	0
Patrick H. Peters, M.D. San Antonio, Texas	190-049	0	0	0	0

Table 19.1-1 Investigators and Financial Disclosure Information

Investigator Name	Study Number	Financial Categories – Amounts in U.S. $			
		1	2	3	4
John F. Pinto, M.D. Las Vegas, Nevada	190-046 190-047	0 0	0 0	0 0	0 0
Paul Pockros, M.D. La Jolla, California	190-013	0	0	0	0
Bryan C. Pogue, M.D. Boise, Idaho	190-049	0	0	0	0
William Privatera, M.D. Austin, Texas	190-047	0	0	0	0
Marc Raphaelson, M.D. Rockville, Maryland	190-046 190-047	0 0	0 0	0 0	0 0
Robert Reid, M.D. San Diego, California	190-049	0	0	0	0
Michele Reynolds, M.D. Dallas, Texas	190-049	0	0	0	0
Robert A. Riesenberg, M.D. Atlanta, Georgia	190-049	0	0	0	0
Dennis Riff, M.D. Anaheim, California	190-048 190-049	0 0	0 0	0 0	0 0
Ernie Riffer, M.D. Phoenix, Arizona	190-048 190-049	0 0	0 0	0 0	0 0
Daniel Rifkin, M.D. Buffalo, New York	190-047	0	0	0	0
Carl Rosenberg, M.D. Cleveland, Ohio	190-026 190-046	0 0	0 0	0 0	0 0
Russell Rosenberg, Ph.D. Atlanta, Georgia	190-026 190-046 190-047 190-048	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0
Sid Rosenblatt, M.D. Irvine, California	190-048 190-049	0 0	0 0	0 0	0 0
Thomas Roth, Ph.D. Detroit, Michigan	190-026 190-046	0 0	0 0	0 0	0 0
John Rubino, M.D. Raleigh, North Carolina	190-048 190-049	0 0	0 0	0 0	0 0
Jon Ruckle, M.D. Tacoma, Washington	190-002	0	0	0	0
Kathleen L. Ryan, M.D. Mt. Laurel, New Jersey	190-046	0	0	0	0
Marshall Sack, M.D. Austin, Texas	190-014	0	0	0	0
R. Bart Sangal, M.D. Troy, Michigan	190-026	0	0	0	0
Paul Saskin, Ph.D., Las Vegas, Nevada	190-046	0	0	0	0

Table 19.1-1 Investigators and Financial Disclosure Information

Investigator Name	Study Number	Financial Categories – Amounts in U.S. $			
		1	2	3	4
Robert B. Schader, M.D. Pembroke Pines, Florida	190-046 190-047	0 0	0 0	0 0	0 0
Kenneth R. Schaefer, M.D. Peoria, Arizona	190-048	0	0	0	0
Martin B. Scharf, Ph.D. Cincinnati, Ohio	190-026 190-045 190-046 190-047 190-048	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Helmut Schmidt, M.D. Dublin, Ohio	190-047	0	0	0	0
Douglas Schumacher, M.D. Columbus, Ohio	190-049	0	0	0	0
Jonathan Schwartz, M.D. Oklahoma City, Oklahoma	190-026 190-046	0 0	0 0	0 0	0 0
Michael Schwartz, M.D. Jupiter, Florida	190-047	0	0	0	0
David Seiden, M.D.1 Miami, Florida	190-046	0	0	0	0
David Seiden, M.D. Pembroke Pines, Florida	190-047 190-048	0 0	0 0	0 0	0 0
Gladstone A. Sellers, M.D. Atlanta, Georgia	190-049	0	0	0	0
Renata Shafor, M.D. San Diego, California	190-026	0	0	0	0
Colin Shapiro, Ph.D.1 Toronto, Ontario, Canada	190-046	0	0	0	0
Ram K. Shrivastava, M.D. New York, New York	190-046	0	0	0	0
Jeffrey S. Simon, M.D. Brown Deer, Wisconsin	190-049	0	0	0	0
Stuart J. Simon, M.D. Austell, Georgia	190-049	0	0	0	0
Thomas M. Snodell, M.D. Mission, Kansas	190-046	0	0	0	0
Thomas Stock, D.O. Evansville, Indiana	190-018	0	0	0	0
Randall Stoltz, M.D. Evansville, Indiana	190-002 190-005	0 0	0 0	0 0	0 0
Danny H. Sugimoto, M.D. Chicago, Illinois	190-049	0	0	0	0
Din-On Sun, D.O. Orlando, Florida	190-014	0	0	0	0
H. Mikel Thomas, M.D. Prairie Village, Kansas	190-048 190-049	0 0	0 0	0 0	0 0

Table 19.1-1 Investigators and Financial Disclosure Information

Investigator Name	Study Number	Financial Categories – Amounts in U.S. $			
		1	2	3	4
Phillip Tigel, M.D.1 Beverly Hills, California	190-046	0	0	0	0
Myron J. Tong, Ph.D., M.D. Pasadena, California	190-013	0	0	0	0
John Trapp, M.D.1 Lincoln, Nebraska	190-046	0	0	0	0
	190-047	0	0	0	0
	190-048	0	0	0	0
Marvin Eugene Vollmer, M.D. Indianapolis, Indiana	190-026	0	0	0	0
James Walsh, Ph.D. Chesterfield, Missouri	190-045	0	0	0	0
J. Catesby Ware, Ph.D.	190-026	0	0	0	0
Norfolk, Virginia	190-046	0	0	0	0
Albert Wauquier, Ph.D. Indianapolis, Indiana	190-046	0	0	0	0
Kenneth Weiss, M.D.	190-048	0	0	0	0
Conshohocken, Pennsylvania	190-049	0	0	0	0
James J. Wellman, M.D.	190-026	0	0	0	0
Atlanta, Georgia	190-045	0	0	0	0
	190-046	0	0	0	0
	190-047	0	0	0	0
Mark Wentworth, M.D. San Antonio, Texas	190-049	0	0	0	0
Philip Westbrook, M.D. Redlands, California	190-046	0	0	0	0
David Winslow, M.D.	190-046	0	0	0	0
Louisville, Kentucky	190-047	0	0	0	0
Gerald D. Wolfley, M.D. Scottsdale, Arizona	190-049	0	0	0	0
Daniel R. Wynn, M.D.	190-046	0	0	0	0
Northbrook, Illinois	190-047	0	0	0	0
Laurence Yellen, M.D. San Diego, California	190-049	0	0	0	0
Gary Zammit, Ph.D.	190-045	0	0	0	0
New York, New York	190-046	0	0	0	0
	190-047	0	0	0	0

Table 19.1-2 lists the research sites, by principal investigator, for whom updated financial disclosure information has not been received nor its absence explained. Two registered letters were sent, and at least one phone call was made requesting updated financial disclosure information. Sepracor continues attempts to obtain updated financial disclosure information for those listed below and will continue to do so until all reasonable efforts to obtain this information are exhausted.

Table 19.1-2 Outstanding Updated Financial Disclosure Information

Investigator Name	Study Number
Arthur Knodel, M.D.	190-026
Carl Rosenberg, M.D.	190-026
Marvin Vollmer, M.D.	190-026

18. User Fee Cover Sheet

This section provides the User Fee Cover Sheet (Form FDA 3397) and a copy of the check that was submitted on January 16, 2003, as payment of the user fee for this application.

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Sepracor Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

2. TELEPHONE NUMBER *(Include Area Code)*

(508) 357-7325

3. PRODUCT NAME

ESTORRA™ (eszopiclone) tablets

4. ~~BLA SUBMISSION TRACKING NUMBER (STN)~~ / NDA NUMBER

N021476

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4268

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

GNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
James A Wachtel	**Executive Director, Regulatory Affairs**	**January 16, 2003**

FORM FDA 3397 (4/01)

SEPRACOR
R&D A/P ACCOUNT
84 WATERFORD DRIVE
MARLBOROUGH, MA 01752

REMITTANCE ADVICE

Check No.

Date : 16-JAN-03 Vendor Name : FOOD AND DRUG ADMINIST Vendor No. : FOODR

FEE ID 4268 NDA 21-476	10-JAN-03		0.00	533,400.00

SEPRACOR
R&D A/P ACCOUNT
84 WATERFORD DRIVE
MARLBOROUGH, MA 01752

Check No. _ _ _

52-153
112

16-JAN-03	$*****533,400.00

Pay Five Hundred Thirty-Three Thousand Four Hundred Dollars And 00 Cents**********

To The Order Of FOOD AND DRUG ADMINISTRATION
PO BOX 360909
PITTSBURGH, PA 15251-6909
United States

AUTHORIZED SIGNATURE

VOID AFTER 180 DAYS

⑈ 24721⑈ ⑆011201539⑆ 00802 18084⑈

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-476	Efficacy Supplement Type SE-	Supplement Number	
Drug: Lunesta		Applicant: Sepracor	
RPM: Renmeet Gujral		HFD- 120	Phone # 301-594-5535

Application Type: ( ) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	Type 1 – NME
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	Februrary 28, 2004
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(x) Paid UF ID number 4268
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No

• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii) N/A
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(x) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "No," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	N/A
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A

❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 2/27/04
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS: 11/10/04, 12/9/03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	11/10/04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	OD:3/4/04 DD: 2/20/04, 12/15/04 MTL: 11/7/03, 11/19,04
❖ Clinical review(s) *(indicate date for each review)*	9/15/03, 10/18/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	11/22/04
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	11/14/03, 12/4/03
❖ Biopharmaceutical review(s) *(indicate date for each review)*	9/23/03, 11/05/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	10/27/04
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	11/10/03
• Bioequivalence studies	
❖ CMC review(s) *(indicate date for each review)*	9/30/03, 10/1/03, 11/6/03, 11/30/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	2/11/04, 11/15/04
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	11/25/03

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

/s/

Renmeet Gujral
1/31/05 10:40:00 AM

Table of Contents
NDA 21-476
Eszopicline Tablets
Used as a Sedative Hypnotic
505(b)(1) Application
User Fee Due Date: December 15, 2004

Volume 1 of 2 – Approval Action Package:

L. Clincal Review

- For this action (10/18/04)
- For Approvable Action (9/15/03)

Volume 2 of 2 – Approval Action Package:

M. Pharmacology/Toxicology Review

- For this action (11/15/04)
- For Approvable Action(2/11/04)
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N. Chemistry Review

- For this action (11/30/04)
- Chemistry Discipline Review Letter (10/1/03)
- For Approvable Action (9/30/03), (11/6/03)

O. Biopharmaceutics Review

- For this Action (11/05/04)
- For Approvable Action (9/23/03)

P. Biometrics Review (no review for this action)

- For Approvable Action
    - 12/4/03
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Q. DMETS Review

- For this action
    - 12/6/04
    - 11/10/04
- For approvable action

R. CSS Review (10/27/04)

S. Microbiology Review (11/22/04)

Locicero, Colleen L

From: Locicero, Colleen L
Sent: Thursday, December 16, 2004 9:19 AM
To: Gujral, Renmeet
Subject: N 21-476

Hi Rimmy,

RT brought in to the office this AM the 2 volumes of the eszopicline action package he had. I could not find the following in the package, and realize they may be in the 3rd volume that you have:

- a completed exclusivity summary (there is a copy of a blank exclusivity summary in volume 1, but I can't find a completed summary
- minutes of the pre-approval safety conference
- a completed peds page (there is a copy of a blank peds page in volume 1, but I can't find a completed page
-ECAC meeting minutes (I see these in DFS, so they are probably in the volume I don't have)
- DSI memo (I see this in DFS, so it is probably in the volume I don't have)

If you could make sure all are in the package before you send to FOI, that'd be great! I'll check with Sandy to see if RT needs these 2 volumes again and if he does not, she'll make arrangements to have these returned to you.

Thanks!
Colleen
443-5383

Locicero, Colleen L

From: Green, Martin
Sent: Tuesday, November 30, 2004 11:47 AM
To: Locicero, Colleen L
Subject: RE: Estorra

Colleen, thanks for asking and I don't need to review the 2nd package.

(On a different note I have made myself the goal of attending at least 2 to 3 divisional meetings per week on upcoming approvals.)

Dave Green

-----Original Message-----
From: Locicero, Colleen L
Sent: Tuesday, November 30, 2004 10:36 AM
To: Green, Martin
Cc: Gujral, Renmeet; Taylor, Richardae
Subject: FW: Estorra

Hi Dave,

The action for the 2nd review cycle for Estorra, an NME developed as a sedative/hypnotic, is due 12/15/04. Rimmy has indicated that the response to our 2/27/04 approvable letter (attached) contains no new pharm/tox info. You reviewed the package for the 1st cycle review (prior to the February AE action). Your comments from that review are attached. Since there is no new pharm/tox info in the response, do you want to review the package for this 2nd action?

Thanks,
Colleen

<< Message: RE: Estorra tertiary reviews >> << File: EstorraAE.pdf >>

-----Original Message-----
From: Gujral, Renmeet
Sent: Monday, November 29, 2004 12:53 PM
To: Locicero, Colleen L
Cc: Oliver, Thomas F; Andreason, Paul J; Katz, Russell G; Taylor, Richardae
Subject: RE: Estorra

I was looking over the email I sent out earlier and I realized I stated there were new pharm/tox issues. I meant to say there are NO pharm/tox issues....
Sorry:)
Rimmy

-----Original Message-----
From: Gujral, Renmeet
Sent: Monday, November 29, 2004 12:29 PM
To: Locicero, Colleen L
Cc: Oliver, Thomas F; Andreason, Paul J; Katz, Russell G; Taylor, Richardae
Subject: RE: Estorra

There are new pharm/tox issues and I am still waiting for the chemistry review. Let me know if you just want it sent to John or both John and Dave. There are no stat reviews from this cycle, and I am expecting the DMETS review hopefully on Wednesday. I am expecting updated labeling from the company on Wednesday. I am out of the office Tomorrow (11/30) thru Thursday (12/2) and will be back in the office on Friday(12/3) morning. Chardae Taylor will be covering for me while I am gone.
Thanks
Rimmy

-----Original Message-----
From: Locicero, Colleen L
Sent: Monday, November 29, 2004 10:55 AM

Gujral, Renmeet

From: Roselle, Nora
nt: Tuesday, November 23, 2004 3:38 PM
: Gujral, Renmeet
Cc: Mahmud, Alina; Andreason, Paul J; Holquist, Carol A; Toyer, Denise P; Beam, Sammie
Subject: NDA 21-476 (Lunesta)

Renmeet,

Attached are the potential names of concern for NDA 21-476 (Lunesta) as per our conversation this afternoon. This email is not an official response to the consult request, an official review in DFS will follow. This email only serves as a preliminary evaluation for your consideration. The name of particular concern is [redacted] Due to the similarity in name and product characteristics (oral tablets, once daily dosing regimen at bedtime, similarly scripted strengths [3 mg vs. 8 mg], patient and prescriber population, and possibly stored in close proximity on pharmacy shelves) between Lunesta and [redacted] we believe that the products may not coexist in the marketplace. The PDUFA date for [redacted] however, if the approval of Lunesta is delayed, the acceptability of the name will have to be reevaluated.

Lunesta.doc (42 KB)

Thank you,

Nora

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety
Center for Drug Evaluation and Research
Phone 301-827-3199

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 11/9/04 **DATE OF DOCUMENT:** 11/8/04	**DESIRED COMPLETION DATE:** 12/9/04 **PDUFA DATE:** 12/15/04	**ODS CONSULT #:** 04-0284

TO: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Renmeet Gujral, PharmD
Project Manager
HFD-120

PRODUCT NAME: **Lunesta** (Eszopiclone Tablets) 1 mg, 2 mg, and 3 mg **NDA#:** 21-476	**NDA SPONSOR:** Sepracor Inc.

SAFETY EVALUATOR: Nora Roselle, PharmD

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Lunesta provided that only one name Lunesta (NDA 21-476) or — , is approved. Due to the similarity in name and product characteristics between Lunesta and — we believe that the products may not coexist in the marketplace. There is a high potential for name confusion especially if both products are introduced into the marketplace in close proximity to each other. The PDUFA date for — is — and the PDUFA date for Lunesta is December 15, 2004. The acceptability of the proposed proprietary name Lunesta depends on which application, Lunesta — receives approval first, as these two names may not co-exist due to their similarities. If the approval of Lunesta is delayed, the acceptability of the name will need to be reevaluated.

2. Updated labels and labeling were not provided for review and comment. DMETS recommends implementation of the label and labeling revisions outlined in outlined in our previous proprietary name review for Esonna (ODS Consult 04-0244).

3. DDMAC finds the proprietary name, Lunesta, acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 22, 2004

NDA#: 21-476

NAME OF DRUG: Lunesta (Eszopiclone Tablets)
1 mg, 2 mg, and 3 mg

NDA HOLDER: Sepracor, Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for assessment of the proprietary name, "Lunesta", regarding potential name confusion with other proprietary or established drug names. The sponsor has submitted additional information, including an independent analysis conducted by the Brand Institute (BI), to DMETS for review and comment. We refer you to ODS Consult 04-0244 for comments on the container labels, carton and insert labeling.

Lunesta is the *fourth* proposed proprietary name for this product. DMETS previously reviewed the names *Estorra, Astorra, and Esonna*, and found these proposed proprietary names unacceptable.

PRODUCT INFORMATION

Lunesta is a nonbenzodiazepine indicated for the treatment of insomnia characterized by difficulty falling asleep, and/or difficulty maintaining sleep during the night and early morning. In controlled outpatient and sleep laboratory studies, Lunesta administered at bedtime decreases sleep latency and improves sleep maintenance. The dose of Lunesta should be individualized. In adult patients, both 2 mg and 3 mg decrease sleep latency, and 3 mg is more effective for sleep maintenance. In elderly patients, both 1 mg and 2 mg decrease sleep latency, and 2 mg is effective for sleep maintenance. Lunesta is available as 1 mg, 2 mg, and 3 mg tablets. The 2 mg and 3 mg strengths are available in bottles of 100 tablets and cartons of 100 tablets. The 1 mg strength is available in bottles of 100 tablets only.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Lunesta to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Lunesta. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Lunesta acceptable from a promotional perspective.

2. The Expert Panel identified seven proprietary names that were thought to have the potential for confusion with Lunesta. Similarly, through further review, three additional drug names, Neulasta, Levitra, and Crestor, were also determined to have potential for confusion with Lunesta. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.
[3] The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, Drugs@FDA, and the electronic online version of the FDA Orange Book.
[4] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com
[5] WWW location http://www.uspto.gov/tmdb/index.html.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by EPD

Evista	Raloxifene Tablets 60 mg	60 mg/day	Look-alike, Sound-alike
			Look-alike
Zavesca	Miglustat Capsules 100 mg	One capsule 3 times daily.	Look-alike, Sound-alike
Arestin	Minocycline HCl Microspheres, Sustained-Release 1 mg (Dry powder packaged in a unit dose cartridge)	Oral health care professional inserts the unit-dose cartridge into the base of the periodontal pocket and expels the powder.	Look-alike
Lustra	Hydroquinone Cream 4 %	Apply to affected skin twice daily	Look-alike, Sound-alike
			Sound-alike
(ANDA 76-812)	Estradiol and Estradiol/Norgestimate Tablets 1 mg and 1 mg/0.09 mg		Look-alike, Sound-alike
Neulasta	Pegfilgrastim Solution for Injection, 6 mg in 0.6 mL single use prefilled syringe	Single 6 mg SC injection administered once per chemotherapy cycle.	Sound-alike
Levitra	Vardenafil HCl Tablets, 2.5 mg, 5 mg, 10 mg, 20 mg	10 mg taken approximately 60 minutes before sexual activity	Look-alike
Crestor	Rosuvastatin 5 mg, 10 mg, 20 mg, and 40 mg	Hyperlipidemia: starting dose - 10 mg once daily; 5 mg for those requiring less aggressive LDL reductions or those predisposed to myopathy Maintenance dose - 5 mg to 40 mg once daily	Look-alike

*Frequently used, not all-inclusive.
NOTE: This review contains proprietary and confidential information that should not be released to the public.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Lunesta were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Lunesta with

marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Lunesta (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Lunesta 3mg 1 po before bedtime #30	Lunesta 3 mg One by mouth before bedtime. Number thirty.
Inpatient RX: Lunesta 3mg before bedtime PRN #30	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. The remaining incorrect name interpretations were misspelled/phonetic variations of "Lunesta". See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Lunesta, the primary concerns related to look-alike and sound-alike confusion with Evista — Zavesca, Arestin, Lustra, — ***, and — Similarly, through further review, three additional drug names, Neulasta, Levitra, and Crestor, were also determined to have potential for confusion with Lunesta.

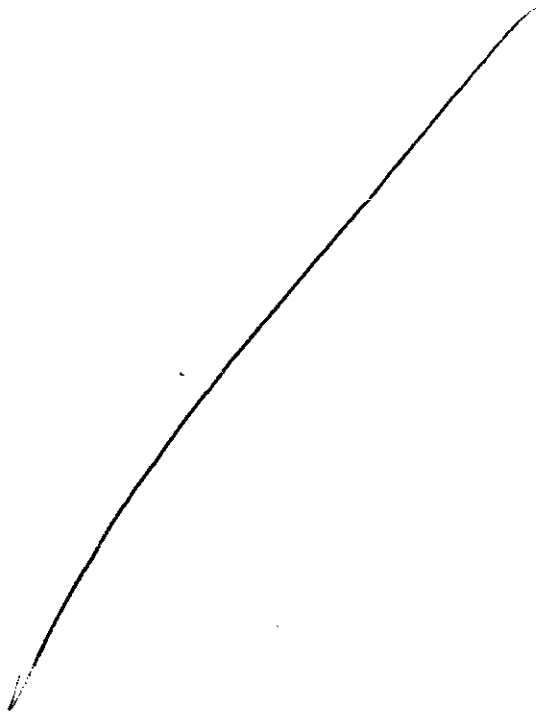
Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Lunesta.

*** Note: This review contains proprietary and confidential information that should not be released to the public.***

1. Evista was identified as having look-alike potential with Lunesta. Evista (raloxifene) is a selective estrogen receptor modulator used in the treatment and prevention of osteoporosis in postmenopausal women. Evista is available as a 60 mg oral tablet and is prescribed as one tablet daily. Evista and Lunesta have some look-alike similarities in that when scripted the letters "Ev" can look like "Lu" (see below). Also, the two names share overlapping ending letters ("sta"). Evista and Lunesta can sound similar as each name contains three syllables ending with the letters "sta". Evista and Lunesta share a common route of administration (oral), dosage form (tablets), and dosing regimen (once daily). Evista is available as a 60 mg tablet whereas Lunesta will be available as a 1 mg, 2 mg, and 3 mg tablet. Although the two products share numerous orthographic similarities, the dispensing pharmacist would have to clarify the dosage strength with the prescriber since there is no overlap in dosage strength. DMETS believes there is decreased risk of confusion and error between Evista and Lunesta.

Lunesta Lunesta

2.



*** Note: This review contains proprietary and confidential information that should not be released to the public.***

3. Zavesca was found to have look- and sound-alike potential with Lunesta. Zavesca is indicated for the treatment of Gaucher Disease. Zavesca is available as a 100 mg oral capsule and is dosed as one capsule three times a day. Zavesca and Lunesta have an orthographic likeness due to the overlapping similarity in strokes of the letters "Zaves" vs. "Lunes" in addition to their similar looking suffixes, "-ca" vs. "-ta"(see sample below). The combination letters at the end of each name ("-esca" vs. "esta") have sound-alike similarities but when pronounced the letters "Za" vs. "Lu", in Zavesca and Lunesta respectively, help differentiate the names verbally. Zavesca and Lunesta have overlapping dosage forms (tablet/capsule) and route of administration (oral). Despite these similarities, there are differences between the two drugs which make it unlikely that confusion would exist. Zavesca and Lunesta have different dosing regimens (once daily at bedtime vs. three times daily), indications for use (insomnia vs. Gaucher Disease), and strengths (1 mg, 2 mg, and 3 mg vs. 100 mg). For the reasons mentioned above, DMETS believes the likelihood for confusion between Zavesca and Lunesta to be minimal.

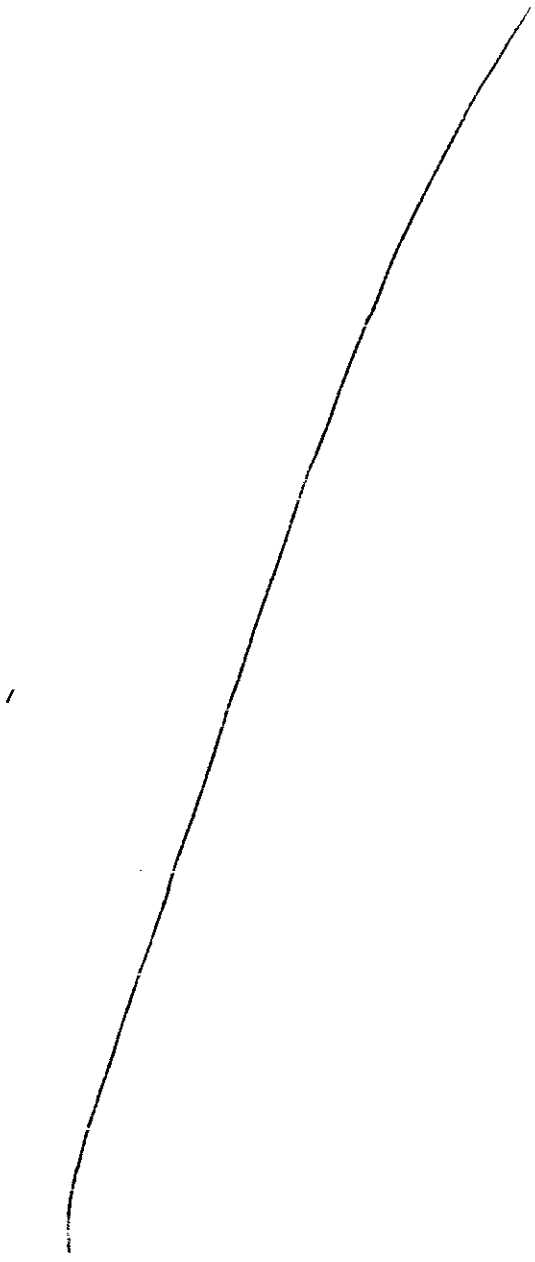
Lunesta Zavesca

4. Arestin was identified to have potential for look-alike confusion with Lunesta. Arestin is indicated for the treatment of adult periodontitis. Arestin is available as a 1 mg dry powder which is packaged in a unit dose cartridge. For drug administration, the oral health care professional inserts the unit-dose cartridge into the base of the periodontal pocket and expels the powder. The two products have orthographic similarity when the letter "A" in Arestin is written in cursive without fully connecting the letter at the top, it can resemble the letters "lu" (see below). In addition, the ending letters of each name ("-estin" vs. "esta") may resemble each other because of similar stroke characteristics. Both Arestin and Lunesta share a common strength (1 mg). However, there are many characteristics which help differentiate the two products. Arestin and Lunesta have different dosing regimens (given at dental appointments vs. once daily at bedtime), dosage form (dry powder vs. tablet), route of administration (injection vs. oral), and indication (periodontitis vs. insomnia). Furthermore, Arestin must be administered by a dentist or other oral health care provider. Therefore, it is less likely that Arestin would be distributed in a retail pharmacy setting, as would Lunesta. Despite orthographic and product similarities, DMETS believes the likelihood for confusion is minimal given the limited distribution of Arestin.

Lunesta Arestin

5. Lustra was identified to have look-alike similarities with Lunesta. Lustra is used in the bleaching of hyperpigmented skin such as freckles and age spots. Lustra is available as a 4% topical cream and is applied to the affected skin areas twice daily. When scripted, the letters "Lus" and "Lun" look similar and each name ends with the letter "a". However, the middle letters ("tr" vs. "est") help differentiate the names as the upstroke of the letter "t" is located as the sixth letter in Lunesta whereas it appears as the fourth letter in Lustra. The two drugs have different dosage forms (cream vs. tablet), route of administration (topical vs. oral), dosing regimens (once daily vs. twice daily), and strengths (4% vs. 1 mg, 2 mg, and 3 mg). DMETS believes that even though the two names share orthographic similarities, the differences mentioned above will help decrease any risk of confusion and error.

Lunesta Lustra



8. Neulasta and Lunesta have the potential for sound-alike confusion. Neulasta is used in the treatment of chemotherapy-induced neutropenia. Neulasta is

*** Note: This review contains proprietary and confidential information that should not be released to the public.***

available as 6 mg in 0.6 mL single-use prefilled syringes. The recommended dose of Neulasta is 6 mg administered as a subcutaneous injection once per chemotherapy cycle. Both Neulasta and Lunesta have three syllables. The beginning of each name rhyme ("Neu-" vs. "Lu") and each ends with the letters "-sta". However, the middle combination of letters ("las" vs. "nes") helps differentiate the two names from one another. Neulasta and Lunesta have different dosage forms (injection vs. tablet), administration schedule (once pre chemotherapy cycle vs. once daily at bedtime), route of administration (subcutaneous vs. oral), strengths (6 mg per 0.6 mL vs. 1 mg, 2 mg, and 3 mg), and different indications for use (neutropenia vs. insomnia). Although the two products have some similarities when spoken, the product differences will help minimize the risk for confusion and error between Neulasta and Lunesta.

9. Levitra was identified to have potential for look-alike confusion with Lunesta. Levitra is indicated for the treatment of erectile dysfunction. Levitra is available as 2.5 mg, 5 mg, 10 mg, and 20 mg oral tablets. The recommended starting dose for Levitra is 10 mg taken approximately 60 minutes before sexual activity. The maximum recommended dosing frequency is once daily. The two products have orthographic similarity as the letters "Lev" in Levitra can resemble the letters "Lun" in Lunesta (see below). However, the ending letters of each name ("-itra" vs. "esta") look different when scripted. Both Levitra and Lunesta share similar numerical strengths (10 mg and 20 mg vs. 1 mg and 2 mg), dosage form (tablet), route of administration (oral), dosing regimen (both can be given once daily). The drugs have different indications for use (erectile dysfunction vs. insomnia). Despite product similarities, DMETS believes the likelihood for confusion is minimal given the lack of look-alike similarity between Levitra and Lunesta.

Levitra Lunesta

10. Crestor was identified to have potential for look-alike confusion with Lunesta. Crestor is indicated for the treatment of hyperlipidemia. Crestor is available in 5 mg,10 mg, 20 mg, and 40 mg oral tablets. The recommended starting dose for Crestor is 10 mg once daily with a recommended dosing range of 5 mg to 40 mg once daily. The two products have orthographic similarity as the letters "Cres" in Crestor can resemble the letters "Lun" in Lunesta (see page 10). However, the ending letters of each name ("-tor" vs. "esta") look different when scripted and help differentiate one name from the other. Both Crestor and Lunesta share similar numerical strengths (10 mg and 20 mg vs. 1 mg and 2 mg), dosage form (tablet), route of administration (oral), dosing regimen (both can be given once daily). The drugs have different indications for use (hyperlipidemia vs. insomnia) and each drug. Despite product similarities, DMETS believes the likelihood for confusion is minimal given the lack of look-alike similarity between Crestor and Lunesta.

Crestor Lunesta

E. INDEPENDENT NAME ANALYSIS

Upon review of the information submitted by the [redacted] the following additional names were identified as potential sound or look-alike products.

1. Similar Drug Name Listing:

   Alluna, Cenestin, Celexa, Evista, Fenestrel, Levitra, Levora, Lovenox, Lumigan, Ludiomil, Lunelle, Lupron, Lustra, Luvox, and Pronestyl were considered to look and sound similar to Lunesta. After further evaluation of the aforementioned names, DMETS concurs that these names do not pose a significant problem due to differentiating product characteristics and/or a lack of convincing look- and sound-alike characteristics.

2. Medical Term Similarity:

   Lumbar, Lunacy, Lunate, Lunatic, Lung, Lupus, Luteal, Lumen, Luminal and Menses were considered to be similar to Lunesta, based on sound and/or appearance. After further review of the aforementioned medical terms, DMETS concurs that these medical terms do not pose a significant problem with the proposed proprietary name, Lunesta.

3. Computer-Assisted Analysis:

   The following twenty-nine names were listed for further consideration due to similarity with Lunesta: Besta, Crestor, Duranest, Estar, E-Vista, Genesa, Jenest-28, Mannest, Menest, Miostat, Monistat, Nestabs, Neulasta, Neumega, and Ranestol. After further evaluation of the aforementioned names, DMETS concurs that these names do not pose a significant problem due to differentiating product characteristics and/or a lack of convincing look- and sound-alike characteristics.

III. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Lunesta provided that only one name Lunesta (NDA 21-476) or —) is approved. Due to the similarity in name and product characteristics between Lunesta and — , we believe that the products may not coexist in the marketplace. There is a high potential for name confusion especially if both products are introduced into the marketplace in close proximity to each other. The PDUFA date for — . is — and the PDUFA date for Lunesta is December 15, 2004. The acceptability of the proposed proprietary name Lunesta depends on which application, Lunesta or — receives approval first, as these two names may not co-exist due to their similarities. If the approval of Lunesta is delayed, the acceptability of the name will need to be reevaluated.

B. Updated labels and labeling were not provided for review and comment. DMETS recommends implementation of the label and labeling revisions outlined in outlined in our previous proprietary name review for Esonna (ODS Consult 04-0244).

C. DDMAC finds the proprietary name Lunesta acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina R. Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A – DMETS Prescription Study Results

Inpatient	Outpatient	Voice
Lisnestra	Lunestra	Lonesta
Lunesta	Lunesta	Lunexa
Usriesta	Lunesta	Lunesta
Lunesta	Lunesta	Lunestra
Lesnesta	Lunesta	Lanesta
Lunesta	Lunestra	Anesta
Lunesta	Lunestra	Enesta
Lunsetra	Lunestra	Lunesta
Lureista	Lunestra	Unesta
Uinestra	Lunesta	Lunesta
Lonesta	Lunesta	Lunesta
Lunestra	Lunestin	Enesta
Lisnesta	Lunesta	Unesta
Lunesta		Zanesta
Lunesta		
Lusnesta		
Lunesta		
Lunestra		
Lunesta		

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/s/

Nora L. Roselle
12/6/04 12:47:55 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
12/6/04 01:05:23 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/6/04 03:14:24 PM
DRUG SAFETY OFFICE REVIEWER

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 18, 2004

To: Dr. Russell G. Katz
Director, Division of Neuropharmacological Drugs. HFD-120

Through: Michael Klein, Ph.D.
Controlled Substance Staff. HFD-009

From: Silvia N. Calderon, Ph.D.
Controlled Substance Staff. HFD-009

Subject: NDA 21-476. — .(eszopiclone) tablets, 2.0 mg and 3.0 mg, Drug Abuse and Dependence section of the proposed label
Sponsor: Sepracor Inc.

This memorandum is a response to a consultation from the Division of Neuropharmacological Drug Products, HFD-120, on the language proposed by the Sponsor under the Drug Abuse and Dependence section of the label, submitted to the Agency on September 30, 2004.

CONCLUSIONS AND RECOMMENDATIONS

- Under the "DRUG ABUSE AND DEPENDENCE" section, "Controlled Substance Class" subsection, modify the Sponsor's statement that currently indicates the control status of , to include an explanatory sentence indicating what other substances are also included in Schedule IV of the Controlled Substances Act. Please note that CSS's proposed language is indicated in bold and deletions are indicated by strikethrough text.

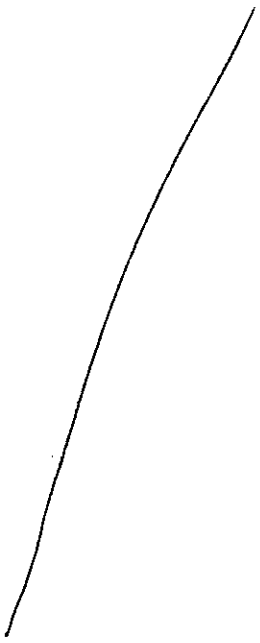
  — A is — a Schedule IV controlled substance —
  under the Controlled Substances Act. Other substances under the same classification are benzodiazepines and the non-benzodiazepine hynotics zaleplon and zolpidem.

- Under the "Abuse, Dependence and Tolerance" section, "Abuse and Dependence" subsection, delete the Sponsor proposed sentence that currently reads, " — CSS reviewed the information submitted in the NDA and consulted the Office of Biostatistics for the

statistical review and evaluation of clinical abuse liability study, Study 190-016. Data from Study 190-016 does not support the claim. As previously discussed in our November 14, 2003 consult, over half of the subjects in each treatment group responded equally to the liking and disliking questions in this study. Answering that the drug effect is neither liked nor disliked is possible. However, answering that the drug effect is liked "an awful lot" and disliked " an awful lot" at the same time suggests that the questionnaire is not valid. The true interpretation of the responses obtained in the study for the Disliking and Liking questions is unclear and fails to support the Sponsor's conclusion. Thus, the Sponsor proposed paragraph should be modified to read:

"In a study of abuse liability, conducted in patients with known histories of abuse, eszopiclone at doses of 6 and 12 mg produced similar to those of diazepam

- Under the "Abuse, Dependence and Tolerance" section, "Abuse and Dependence" subsection, include a



- Under the "Abuse, Dependence and Tolerance" section, "Abuse and Dependence" subsection, modify the proposed last paragraph to include similar wording to the one used in zopiclone labels from other countries. Additions are indicated in bold and deletions are indicated by strikethrough text.

- Regarding tolerance and withdrawal signs, abuse liability studies are single dose studies and therefore are not designed to capture physical dependence and tolerance. Nevertheless, it is suggested to incorporate in the label, under the "Tolerance" subsection, general language similar to the one use in the zopiclone labels regarding the potential loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like hypnotics, such as eszopiclone after repeated use for a few weeks. The following paragraph is suggested:

  "Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use of these drugs for a few weeks."

- Please refer to the APPENDIX section of this consult for suggested CSS's recommendations.

2 Draft Labeling Page(s) Withheld

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/s/

Silvia Calderon
10/27/04 01:25:27 PM
CHEMIST

Michael Klein
10/27/04 01:42:02 PM
CHEMIST
Acting Director for Deborah Leiderman, MD, Director, Controlled Substance Staff

43 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-476

DISCIPLINE REVIEW LETTER

Sepracor Inc.
Attention: Mohammed A. Salem, Ph.D., RAC
Director, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752-7010

Dear Dr. Salem:

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

We also refer to your submissions dated March 17, 2003 and July 15, 2003.

Our review of the Chemistry, Manufacturing and controls section of your submission is complete, and we have identified the following deficiencies:

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 — for 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 — testing 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 (— , 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**

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

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Merril Mille, Consumer Safety Officer, at (301) 594-5528.

Sincerely,

Thomas Oliver, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products, HFD-120
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research