

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-476**

**Chemistry Review(s)**

**NDA 21-476**

**Estorra™ (Eszopiclone) Tablets**

**Sepracor Inc.**

**Gurpreet Gill-Sangha, Ph.D.**

***DIVISION OF NEUROPHARMACOLOGICAL DRUG  
PRODUCTS***

**Review of Chemistry, Manufacturing, and Controls**

# Table of Contents

<b>DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS.....</b>	<b>1</b>
<b>Table of Contents.....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>5</b>
<b>The Executive Summary.....</b>	<b>9</b>
I. Recommendations .....	9
A. Recommendation and Conclusion on Approvability .....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	11
<b>Chemistry Assessment.....</b>	<b>12</b>
I. DRUG SUBSTANCE.....	12
1. Description & Characterization.....	13
a. Description.....	13
b. Characterization / Proof Of Structure .....	13
2. Manufacturer.....	13
3. Synthesis / Method Of Manufacture .....	13
a. Starting Materials - Specs & Tests.....	13
b. Solvents, Reagents, etc.....	14
c. Flow Chart.....	14
d. Detailed Description .....	14
4. Process Controls .....	15
a. Reaction Completion / Other In-Process Tests .....	15
6. Regulatory Specifications / Analytical Methods .....	19
a. Drug Substance Specifications & Tests.....	19
b. Purity Profile.....	21
c. Microbiology .....	23
7. Container/Closure System For Drug Substance Storage.....	23
8. Drug Substance Stability .....	23

Chemistry Assessment Section

II. DRUG PRODUCT.....29

    1/2. Components/Composition.....30

    3. Specifications & Methods For Drug Product Ingredients.....31

        a. Active Ingredient(s).....31

        b. Inactive Ingredients.....31

    4. Manufacturer.....32

    5. Methods Of Manufacturing And Packaging .....32

        a. Production Operations.....32

        c. Reprocessing Operations.....33

    6. Regulatory Specifications And Methods For Drug Product.....33

        a. Sampling Procedures.....33

        b. Regulatory Specifications And Methods.....34

    7. Container/Closure System.....39

    8. Microbiology.....40

    9. Drug Product Stability.....40

III. INVESTIGATIONAL FORMULATIONS.....43

IV. ENVIRONMENTAL ASSESSMENT .....43

V. METHODS VALIDATION .....44

VI. LABELING.....44

VII. ESTABLISHMENT INSPECTION.....47

VIII. COMMENTS FOR SEPRACOR.....48

# TRY REVIEW TEN

## Chemistry Assessment Section

### List of Tables

Table 1: Updated Drug Substance Specifications .....	12
Table 2: Updated Specifications of ' — .....	16
Table 3: Analytical Data for Current Eszopiclone Reference Standard** .....	18
Table 4: Eszopiclone Batch Analysis Data for Batches Manufactured Using (RS)-zopiclone from ~ .....	22
Table 5: Summary For Release Data for Eighteen Drug Substance Batches Manufactured from (RS)- zopiclone form — .....	23
Table 6: ~ Degradation Impurities from New Developmental — Studies .....	26
Table 7: Proposed Drug Substance — .....	27
Table 8: Updated Drug Product Specifications .....	29
Table 9: 1.0 mg Strength Estorra Tablet Unit Dose Composition .....	30
Table 10: Equipment Used to Manufacture Estorra Tablets <sup>1</sup> .....	32
Table 11: Typical Sampling Plan for — .....	34
Table 12: Impurity Reference Material Sources .....	35
Table 13: Release Data for 1 mg Strength ~ Tablets .....	36
Table 14: Release Data for 1 mg Strength Light Blue Tablets .....	37
Table 15: Comparison of the ~ and ~ (light blue coated) 1 mg Batches .....	37
Table 16: Specifications for ~ bags for Bulk Storage .....	39
Table 17: Stability protocol for 1 mg tablets for 100 tablets/ ~ bottle at 25 °C/60%RH .....	42
Table 18: Summary of Stability Data for ~ 1 mg at 25 °C/60%RH and 40 °C/75%RH .....	42

### List of Figures

Figure 1: Impurity Chromatogram for Batch 029 0030 Manufactured with (RS)-zopiclone from — .....	20
Figure 2: Impurity Chromatogram for Batch 029 0029, Manufactured with (RS)-zopiclone from ~ .....	20
Figure 3: Impurity Chromatogram for Batch 029 0035, Manufactured with (RS)-zopiclone from ~ .....	21
Figure 4: Typical — Solution for Method — to Include — .....	35
Figure 5: List of Reference Standards for Estorra Tablets .....	44
Figure 6: Representative — Carton Label .....	46
Figure 7: Revised Bottle Label (representation shown for 1 mg) .....	46

Appears This Way  
On Original

# Chemistry Review Data Sheet

1. NDA 21-476
2. REVIEW #: 3
3. REVIEW DATE: November 29, 2004
4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	January 31, 2003
N(BC) Amendment	March 17, 2003
N(C) Amendment	June 5, 2003
N(C) Amendment	June 24, 2003
N(BL) Amendment	July 15, 2003
N(C) Amendment	July 25, 2003
CMC review #1 (approvable)	September 30, 2003
CMC Discipline Review Letter	October 1, 2003
CMC review #2 (approvable)	November 6, 2003
FDA AE (approvable) letter	February 27, 2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
BC amendment	February 6, 2004
AZ amendment	June 14, 2004
C Amendment	August 11, 2004
BC Amendment	August 20, 2004
BC Amendment	August 26, 2004
BC Amendment	September 29, 2004
BC Amendment	November 8, 2004
BC Amendment	November 9, 2004
E-mail	November 24, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Sepracor Inc.

Address: 84 Waterford Drive, Marlborough, MA 01752-7010

Representative: Prabhu Nambiar, Ph.D., RAC, Senior Director, Regulatory Affairs

Telephone: (508) 357-7457

# DRUG REVIEW TEST

## Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Estorra™
- b) Non-Proprietary Name (USAN): Eszopiclone
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Treatment of insomnia

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 1, 2 and 3 mg

13. ROUTE OF ADMINISTRATION: Oral

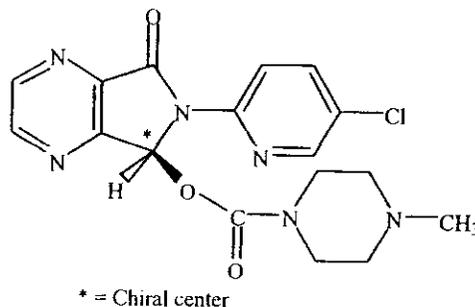
14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed  
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name:	1-Piperazinecarboxylic acid, 4-methyl-(5S)-6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester
USAN Name:	(+)-(5S)-6-(chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl-4-methylpiperazine-1-carboxylate
Non-Proprietary Name:	Eszopiclone
Chemical Formula:	C <sub>17</sub> H <sub>17</sub> ClN <sub>6</sub> O <sub>3</sub>
Molecular Weight:	388.81
CAS registry #:	138729-47-2
Structure:	



**DRUG REVIEW TABLE**

Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
-	II	}	(RS)- zopiclone	1	Inadequate	July 15, 2003	Deficiency Letter sent
					Adequate	September 3, 2004	
-	II	}	(RS)-zopiclone	1	Inadequate	July 23, 2003	Deficiency letter sent
					Adequate	September 17, 2004	
-	II	}	(RS)-zopiclone	1	Inadequate	June 23, 2003	Deficiency letter sent
					Adequate	August 31, 2004	

Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: NA**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 58,647	Commercial IND from Sepracor for (S)-zopiclone oral solution for treatment of insomnia. Active as of December 4, 2000
IND	IND /	/
IND	IND /	/

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	November 14, 2003	Ohidul Siddiqui
EES	Acceptable	November 18, 2004	FDA Compliance
Pharm/Tox	Pending		Aisar Atrakchi, Ph.D.
Biopharm	Acceptable	September 23, 2003	Andre Jackson, Ph.D.
LNC	USAN available	NA	

**CHEMISTRY REVIEW TABLE**

## Chemistry Assessment Section

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Methods Validation	Acceptable	As per Chemistry review #1 dated September 30, 2003	Gurpreet Gill-Sangha, Ph.D.
OPDRA	Pending		
EA	Acceptable, categorical exclusion granted as per information from Sepracor	As per this review for all strengths (1, 2 and 3 mg)	Gurpreet Gill-Sangha, Ph.D.
Microbiology	Acceptable	November 23, 2004	James McVey, Ph.D.

**APPEARS THIS WAY  
ON ORIGINAL**



## STABILITY REVIEW TEM

### Chemistry Assessment Section

(RS)-zopiclone at either the \_\_\_\_\_ or the Sepracor site at Nova Scotia, Canada. The packaging and testing is also performed at the \_\_\_\_\_ or Sepracor sites. The DMF's for (RS)-zopiclone were reviewed again during this review cycle and found to be adequate by Dr. Gurpreet Gill-Sangha. Sepracor has provided stability data for 24 months for 25 C/60%RH and 30 C/60%RH conditions. A \_\_\_\_\_ re-test date for drug substance is granted based on acceptable real-time stability data (refer to drug substance stability section for justification). The specifications for eszopiclone are also updated to reflect addition of \_\_\_\_\_ new impurities \_\_\_\_\_, changes in particle size for \_\_\_\_\_, changes in levels of \_\_\_\_\_ and incorporation of \_\_\_\_\_ and lowering of microbiological specifications. The updated drug substance specifications are listed at the beginning of the drug substance section of this review.

The drug product, Estorra tablets, is formulated as film coated tablets for oral administration in the 1, 2 and 3 mg strengths. The \_\_\_\_\_ contains active eszopiclone with microcrystalline cellulose, \_\_\_\_\_ calcium phosphate, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate which are all either NF or USP technical grade.

\_\_\_\_\_ blue for 3 mg tablets. The commercial batch size may range up to \_\_\_\_\_ (tablets). Estorra tablets are manufactured, packaged and tested by the contractor Pantheon Inc., Mississauga, Ontario, Canada. The tablets are manufactured by the \_\_\_\_\_ film coat. The updated stability data was provided for 2 and 3 mg strengths, and based on the data a 24 month expiry is granted for the 2 and 3 mg strengths in \_\_\_\_\_ bottles and \_\_\_\_\_. Based on \_\_\_\_\_ of stability data provided for commercial light blue 1 mg strength and supportive data for \_\_\_\_\_ 1 mg strength, a 15 month expiry is granted for 1 mg in \_\_\_\_\_ bottles. At the time of this review, no information about 1 mg \_\_\_\_\_ is provided and as stated by Sepracor the information will be provided as a supplement to the NDA.

Four different strengths 1, 1.5, 2 and 3 mg were used for the purpose of investigational formulations. The 2 and 3 mg formulations are identical to the proposed commercial product and the 1 and 1.5 are essentially identical to the proposed 2 mg commercial product with \_\_\_\_\_ to offset the incremental difference in active ingredient. In addition to the tablet formulations, oral solution formulations were used in some clinical studies consisting of aqueous solutions of eszopiclone and sodium phosphate buffer. Except for the change from oral solution to tablet formulations, no other formulation changes occurred during development.

#### B. Description of How the Drug Product is Intended to be Used

The recommended dose for Estorra tablets is \_\_\_\_\_ daily before bedtime. The dose is \_\_\_\_\_ for the elderly and patients with severe hepatic impairment. The

## Chemistry Assessment Section

total daily dose should not exceed 3 mg. Estorra is intended for the treatment of insomnia characterized by difficulty falling asleep, and/or difficulty maintaining sleep during the night and early morning. Estorra is proposed to decrease sleep latency and improve sleep maintenance. Estorra is packaged in 1, 2 and 3 mg in 100 count per bottle

The storage condition is at 25 °C (77 °F) with excursions permitted to 15° to 30 °C (59 to 86 °F).

**C. Basis for Approvability or Not-Approval Recommendation**

NDA 21-476 for Estorra (eszopiclone) tablets is recommended for **APPROVAL** from the CMC standpoint based on the following:

- ◆ Acceptable overall recommendation from FDA Compliance regarding cGMP status of manufacturing, packaging, controls and testing facilities.
- ◆ Adequate responses to CMC concerns related to the drug substance and drug product sections as evaluated in this review. Refer to final updated drug substance and drug product specifications at the beginning of drug substance and drug product sections of this review.

The following comments are to be conveyed to the sponsor:

1. A re-test date for eszopiclone drug substance is granted.
2. A 24 month expiry is granted for the 2 and 3 mg strength tablets in bottles
3. A 15 month expiry is granted for the 1 mg light blue tablet in bottles.

**III. Administrative**

Reviewer – Gurpreet Gill-Sangha, Ph.D.  
Chemistry Team Leader – Thomas Oliver, Ph.D.  
Project Manager – Renmeet Gujral, R.Ph.

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

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CMC review #3 for NDA 21-476

Thomas Oliver  
11/30/04 10:35:15 AM  
CHEMIST

**NDA 21-476**

**Estorra™ (Eszopiclone)**

**Sepracor Inc.**

**Gurpreet Gill-Sangha, Ph.D.**

***DIVISION OF NEUROPHARMACOLOGICAL DRUG  
PRODUCTS***

**Review of Chemistry, Manufacturing, and Controls**

# Table of Contents

<b>DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS.....</b>	<b>1</b>
<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>8</b>
<b>I. Recommendations.....</b>	<b>8</b>
A. Recommendation and Conclusion on Approvability .....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
<b>II. Summary of Chemistry Assessments.....</b>	<b>8</b>
A. Description of the Drug Product(s) and Drug Substance(s) .....	8
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	10
<b>III. Administrative.....</b>	<b>10</b>
<b>Chemistry Assessment .....</b>	<b>11</b>
<b>VII. ESTABLISHMENT INSPECTION .....</b>	<b>11</b>
<b>VIII. DRAFT DEFICIENCY LETTER.....</b>	<b>20</b>

# Chemistry Review Data Sheet

1. NDA 21-476
2. REVIEW #: 2
3. REVIEW DATE: November 6, 2003
4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.
5. PREVIOUS DOCUMENTS: None

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

January 31, 2003

N(BC) Amendment

March 17, 2003

N(C) Amendment

June 5, 2003

N(C) Amendment

June 24, 2003

N(BL) Amendment

July 15, 2003

N(C) Amendment

July 25, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:

Sepracor Inc.

Address:

84 Waterford Drive, Marlborough, MA 01752-7010

Representative:

Mohammed A. Salem, Ph.D., RAC, Director, Regulatory Affairs

Telephone:

(508) 357-7815

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Estorra™
- b) Non-Proprietary Name (USAN): Eszopiclone
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):

# CHEMISTRY REVIEW

## Executive Summary Section

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Treatment of insomnia

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 2 and 3 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed  
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT:

CA Name: 1-Piperazinecarboxylic acid, 4-methyl-(5S)-6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester

USAN Name: (+)-(5S)-6-(chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl-4-methylpiperazine-1-carboxylate

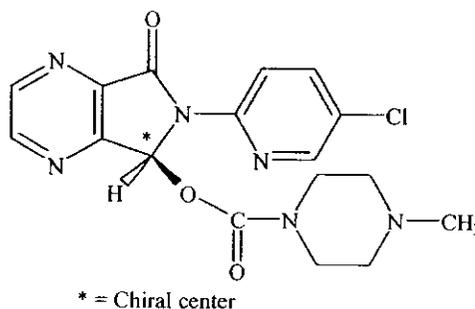
Non-Proprietary Name: Eszopiclone

Chemical Formula:  $C_{17}H_{17}ClN_6O_3$

Molecular Weight: 388.81

CAS registry #: 138729-47-2

Structure:



**CHEMISTRY REVIEW**

Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Refer to Chemistry Review #1

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT	
-	II	/	(RS)- zopiclone	1	Inadequate	July 15, 2003	Deficiency Letter sent	
-	II		(RS)-zopiclone	1	Inadequate	July 23, 2003	Deficiency letter sent	
-	II		(RS)-zopiclone	1	Inadequate	June 23, 2003	Deficiency letter sent	
-	III		/	/	4	Adequate	See CMC review #1	
-	IV		/	/	4	Adequate	See CMC review #1	
-	III		/	/	4	Adequate	See CMC review #1	
-	III		/	/	4	Adequate	See CMC review #1	
-	III		/	/	4	Adequate	See CMC review #1	
-	III		/	/	4	Adequate	See CMC review #1	
-	III		/	/	4	Adequate	See CMC review #1	

# CHEMISTRY REVIEW

## Executive Summary Section

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
-	III	/	/	4	Adequate	See CMC review #1	
-	III	/	/	4	Adequate	See CMC review #1	
-	III	/	/	4	Adequate	See CMC review #1	
-		/	/	4	Adequate	See CMC review #1	
-	III	/	/	4	Adequate	See CMC review #1	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**CHEMISTRY REVIEW**

## Executive Summary Section

**B. Other Documents: NA**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 58,647	Commercial IND from Sepracor for (S)-zopiclone oral solution for treatment of insomnia. Active as of December 4, 2000
IND	IND	
IND	IND	

**18. STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		
EES	Acceptable	November 5, 2003	FDA Compliance
Pharm/Tox	Pending		
Biopharm	Acceptable	September 23, 2003	Andre Jackson, Ph.D.
LNC	USAN available	NA	
Methods Validation	Pending		
OPDRA	Pending		
EA	Acceptable as per Chemistry Review #1	September 29, 2003	Gurpreet Gill-Sangha, Ph.D.
Microbiology	NA		

# The Chemistry Review for NDA 21-411

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

N 21-476 for Estorra™ (eszopiclone) tablets is recommended **APPROVABLE** from the CMC standpoint. The approval from the CMC standpoint is contingent on adequate responses to CMC deficiencies as noted in this review. FDA Compliance has an overall acceptable cGMP recommendation Compliance for all the manufacturing, packaging and testing sites as of November 5, 2003.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Estorra™ (eszopiclone) tablets, a nonbenzodiazepine anti-insomnia agent, for the treatment of insomnia is to be marketed as a 2 and 3 mg strengths in bottles containing 100 dosage units per bottle.

The 3 mg tablet is round, blue film-coated while the 2 mg tablet is round, white film-coated.

The drug substance eszopiclone is a white to light yellow crystalline solid and is It has a single chiral center with (S)-configuration at the 5-position bearing the 4-methyl-1-piperidine carboxylate substituent. Eszopiclone is slightly soluble in ethanol, very slightly soluble in water, soluble in phosphate buffer pH 3.2,

form of eszopiclone (molecular weight 388.81) was found by using

The particle size of eszopiclone is between (RS)-zopiclone is purchased from any of the three suppliers which are a (DMF and (DMF). Eszopiclone drug substance is manufactured from (RS)-zopiclone at either the or the Sepracor site at Nova

Executive Summary Section

Scotia, Canada. The packaging and testing is also performed at the — or Sepracor sites. The DMF's for (RS)-zopiclone were reviewed and found deficient by Dr. Gurpreet Gill-Sangha and deficiency letters were sent to all three DMF suppliers. Sepracor has provided stability data for 24 months. The deficiencies in the drug substance section are related to additional information on manufacture of eszopiclone, specifications for raw materials and intermediates and drug substance for impurities — and stability protocol for future batches of eszopiclone.

The drug product, Estorra tablets, is formulated as film coated tablets for oral administration in the 2 and 3 mg strengths. The — contains active eszopiclone with microcrystalline cellulose, — calcium phosphate, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate which are all either NF or USP technical grade.

— olue for the — 3 mg tablets, respectively. The commercial batch size may range up to — .s). Estorra tablets are manufactured, packaged and tested by the contractor Pantheon Inc., Mississauga, Ontario, Canada. The tablets are manufactured by the — film coat. Primary stability data include — for — 2 mg batches and — for — 3 mg batches in — bottles for commercial packs. In addition — accelerated data was provided for samples in bottles. — ambient and — accelerated data was provided for — 2 mg batches in

Impurities: — were not monitored during release and stability. Other deficiencies in the drug product section relate to additional information on manufacturing, overages, impurities and microbial specifications at release and on stability. Changes in the description section of package insert and storage statement for container and carton labels are recommended.

Four different strengths 1, 1.5, 2 and 3 mg were used for the purpose of investigational formulations. The 2 and 3 mg formulations are identical to the proposed commercial product and the 1 and 1.5 are essentially identical to the proposed 2 mg commercial product with — to offset the incremental difference in active ingredient. In addition to the tablet formulations, oral solution formulations were used in some clinical studies consisting of aqueous solutions of eszopiclone and sodium phosphate buffer. Except for the change from oral solution to tablet formulations, no other formulation changes occurred during development.

**B. Description of How the Drug Product is Intended to be Used**

The recommended dose for Estorra tablets is — daily before bedtime. The dose is — for the elderly and patients with severe hepatic impairment. The total daily dose should not exceed 3 mg. Estorra is intended for the treatment of insomnia characterized by difficulty falling asleep, and/or difficulty maintaining sleep during the night and early morning. Estorra is proposed to decrease sleep latency and improve sleep maintenance. Estorra is packaged in — bottles in 100 count per bottle —. The storage condition is at 25 °C (77 °F) with excursions permitted to 15° to 30 °C (59 to 86 °F).

**C. Basis for Approvability or Not-Approval Recommendation**

NDA 21-476 for Estorra (eszopiclone) tablets is recommended **APPROVABLE** from the CMC standpoint based on the adequate responses to CMC concerns related to the drug substance and drug product sections as listed on pages 20-22 of this review. The FDA Compliance has issued an overall acceptable recommendation regarding cGMP status of manufacturing, packaging, controls and testing facilities on November 5, 2003.

**III. Administrative**

Reviewer – Gurpreet Gill-Sangha, Ph.D.  
Chemistry Team Leader – Thomas Oliver, Ph.D.  
Project Manager – Merrill Mille, R.Ph.

12 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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Gurpreet Gill-Sangha  
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CMC Review 2 for NDA 21-476

Thomas Oliver  
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CHEMIST

**NDA 21-476**

**Estorra™ (Eszopiclone)**

**Sepracor Inc.**

**Gurpreet Gill-Sangha, Ph.D.**

***DIVISION OF NEUROPHARMACOLOGICAL DRUG  
PRODUCTS***

**Review of Chemistry, Manufacturing, and Controls**

# Table of Contents

<b>DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS.....</b>	<b>1</b>
<b>Table of Contents.....</b>	<b>2</b>
<b>Chemistry Review Data Sheet .....</b>	<b>6</b>
<b>The Executive Summary.....</b>	<b>11</b>
I. Recommendations .....	11
A. Recommendation and Conclusion on Approvability .....	11
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .....	11
II. Summary of Chemistry Assessments.....	11
A. Description of the Drug Product(s) and Drug Substance(s) .....	11
B. Description of How the Drug Product is Intended to be Used.....	13
C. Basis for Approvability or Not-Approval Recommendation.....	13
III. Administrative.....	13
<b>Chemistry Assessment .....</b>	<b>14</b>
I. DRUG SUBSTANCE.....	14
1. Description & Characterization.....	14
a. Description .....	14
b. Characterization / Proof Of Structure .....	15
2. Manufacturer.....	22
3. Synthesis / Method Of Manufacture .....	23
a. Starting Materials - Specs & Tests.....	23
b. Solvents, Reagents, etc.....	23
c. Flow Chart.....	24
d. Detailed Description .....	24
4. Process Controls .....	26
a. Reaction Completion / Other In-Process Tests .....	26
6. Regulatory Specifications / Analytical Methods .....	30
a. Drug Substance Specifications & Tests.....	30
b. Purity Profile.....	41
c. Microbiology .....	46
7. Container/Closure System For Drug Substance Storage .....	46
8. Drug Substance Stability.....	46

II. DRUG PRODUCT.....	52
1/2. Components/Composition.....	52
3. Specifications & Methods For Drug Product Ingredients.....	55
a. Active Ingredient(s).....	55
b. Inactive Ingredients.....	55
4. Manufacturer.....	56
5. Methods Of Manufacturing And Packaging.....	56
a. Production Operations.....	56
c. Reprocessing Operations.....	60
6. Regulatory Specifications And Methods For Drug Product.....	60
a. Sampling Procedures.....	60
b. Regulatory Specifications And Methods.....	60
7. Container/Closure System.....	72
8. Microbiology.....	72
9. Drug Product Stability.....	73
III. INVESTIGATIONAL FORMULATIONS.....	79
IV. ENVIRONMENTAL ASSESSMENT.....	82
V. METHODS VALIDATION.....	82
VI. LABELING.....	83
VII. ESTABLISHMENT INSPECTION.....	88
VIII. DRAFT DEFICIENCY LETTER.....	96

List of Tables

Table 1: Solubility of Eszopiclone	15
Table 2: Eszopiclone Elemental Analysis	16
Table 3: Eszopiclone	17
Table 4: Eszopiclone	18
Table 5: Eszopiclone	19
Table 6: Eszopiclone	20
Table 7: Typical Equipment for Eszopiclone Drug Substance Manufacture	25
Table 8: Eszopiclone Drug Substance In-Process Controls	26
Table 9: Intermediate/Auxiliary Material Specifications (copied from NDA, Vol. 1.1, page 35)	27
Table 10: Analytical Data for Current Eszopiclone Reference Standard	29
Table 11: Eszopiclone Drug Substance Specifications	30
Table 12: Eszopiclone Related Substances Structures and Sources	31
Table 13: Particle Size Data for Eszopiclone Drug Substance	32
Table 14: Eszopiclone Drug Substance Batch Analysis Data for Batches Manufactured at Sepracor (pages 545-548, Vol. 1.2)	42
Table 15: Eszopiclone Drug Substance Batch Analysis Data for Batches Manufactured at (pages 549-552, Vol. 1.2)	44
Table 16: Specifications for Bags	46
Table 17: Stability Protocol Summary for Primary Stability Studies (page 561, Vol. 1.2)	47
Table 18: Summary of Drug Substance Stability Studies (page 9, July 15, 2003 amendment)	47
Table 19: Summary of Stability Data for Drug Substance Batches for 24 months at 25 °C/60%RH	48
Table 20: Summary of Stability Data for Drug Substance Batches for at 40 °C/75%RH	48
Table 21: Summary of Stability Data for Drug Substance Batches for at 25 °C/60%RH	49
Table 22: Summary of Stability Data for Drug Substance Batches for at 40 °C/75%RH	49
Table 23: Unit Dose Composition for Estorra Tablets 2 and 3 mg	53
Table 24: Estorra Drug Product Batch Compositions (page 6, Vol. 1.3)	54
Table 25: Functions of Inactive Ingredients in Estorra Tablets	54
Table 26: Manufacturing, Testing, Packaging Sites for Estorra Tablets	56
Table 27: Drug Product In-process Controls (page 49, Vol. 1.3)	59
Table 28: Drug Product In-Process Sampling	59
Table 29: Proposed Regulatory Specifications for Estorra Tablets (page 51, Vol. 1.3)	61
Table 30: Batch Analysis Data for 2.0 mg Strength Drug Product Batches	68
Table 31: Batch Analysis Data for 3.0 mg Strength Drug Product Batches	70
Table 32: Overview of Drug Product Stability Protocol	73
Table 33: Primary Stability Study Summary Table for 2.0 mg tablets	74
Table 34: Primary Stability Study Summary for 3.0 mg Tablets	74
Table 35: Supportive Stability Study Summary for 2.5 mg Tablets	75
Table 36: Supportive Stability Study Summary for 3.5 mg Tablets	75
Table 37: Summary of Primary Stability Batches Data for 100 count/ bottles <sup>1</sup>	76
Table 38: Summary of Primary Stability Batches Data for 2 mg	76
Table 39: Summary of data and Supportive Stability Data <sup>1</sup>	77
Table 40: Future Stability Protocol for Estorra Tablets (2.0 and 3.0 mg) at 25 °C/60%RH	78
Table 41: Future Stability Protocol for Estorra Tablets (2.0 and 3.0 mg) at 40 °C/75%RH	78
Table 42: Manufacturing Information for Tablet Investigational Formulations	79
Table 43: Summary of Investigational Formulations Used in Clinical Studies	80

**List of Figures**

<b>Figure 1: Structure of Eszopiclone</b>	<b>16</b>
<b>Figure 2: Eszopiclone UV Spectrum</b>	<b>16</b>
<b>Figure 3: Eszopiclone IR Spectrum</b>	<b>17</b>
<b>Figure 4: Eszopiclone — Spectrum</b>	<b>18</b>
<b>Figure 5: Eszopiclone with Carbon Numbering</b>	<b>18</b>
<b>Figure 6: Eszopiclone — Spectra</b>	<b>19</b>
<b>Figure 7: Eszopiclone — Spectrum</b>	<b>20</b>
<b>Figure 8: — Diagram of Eszopiclone</b>	<b>20</b>
<b>Figure 9: Typical — Spectrum of Eszopiclone</b>	<b>21</b>
<b>Figure 10: Overview of Eszopiclone Synthesis</b>	<b>24</b>
<b>Figure 11: — of Eszopiclone</b>	<b>51</b>
<b>Figure 12: Process Flow Diagram for Manufacture of Eszopiclone (page 11, Vol. 1.3)</b>	<b>58</b>

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# Chemistry Review Data Sheet

1. NDA 21-476
2. REVIEW #: 1
3. REVIEW DATE: September 29, 2003
4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.
5. PREVIOUS DOCUMENTS: None

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original	January 31, 2003
N(BC) Amendment	March 17, 2003
N(C) Amendment	June 5, 2003
N(C) Amendment	June 24, 2003
N(BL) Amendment	July 15, 2003
N(C) Amendment	July 25, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Sepracor Inc.

Address: 84 Waterford Drive, Marlborough, MA 01752-7010

Representative: Mohammed A. Salem, Ph.D., RAC, Director, Regulatory Affairs

Telephone: (508) 357-7815

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Estorra™
- b) Non-Proprietary Name (USAN): Eszopiclone
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):

# CHEMISTRY REVIEW

## Executive Summary Section

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Treatment of insomnia

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 2 and 3 mg

13. ROUTE OF ADMINISTRATION: Oral

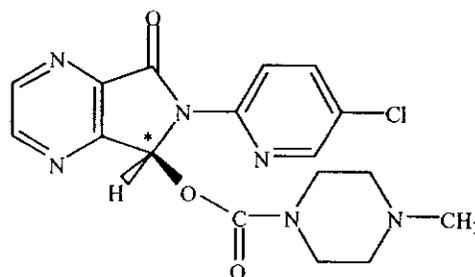
14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

SPOTS product – Form Completed  
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT:

CA Name: 1-Piperazinecarboxylic acid, 4-methyl-(5S)-6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester  
USAN Name: (+)-(5S)-6-(chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl-4-methylpiperazine-1-carboxylate  
Non-Proprietary Name: Eszopiclone  
Chemical Formula:  $C_{17}H_{17}ClN_6O_3$   
Molecular Weight: 388.81  
CAS registry #: 138729-47-2  
Structure:



\* = Chiral center

# CHEMISTRY REVIEW

## Executive Summary Section

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
-	II	/	(RS)- zopiclone	1	Inadequate	July 15, 2003	Deficiency Letter sent
-	II		(RS)-zopiclone	1	Inadequate	July 23, 2003	Deficiency letter sent
-	II		(RS)-zopiclone	1	Inadequate	June 23, 2003	Deficiency letter sent
-	III			4	Adequate	A per this review	
✓	IV			4	Adequate	As per this review	
-	III			4	Adequate	As per this review	
-	III			4	Adequate	As per this review	
-	III			4	Adequate	As per this review	
-	III			4	Adequate	As per this review	
-	III			4	Adequate	As per this review	

# CHEMISTRY REVIEW

## Executive Summary Section

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
	III			4	Adequate	As per this review	
	III			4	Adequate	As per this review	
	III			4	Adequate	As per this review	
				4	Adequate	As per this review	
	III			4	Adequate	As per this review	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**CHEMISTRY REVIEW**

## Executive Summary Section

**B. Other Documents: NA**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 58,647	Commercial IND from Sepracor for (S)-zopiclone oral solution for treatment of insomnia. Active as of December 4, 2000
IND	IND —	
IND	IND —	

## 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		
EES	Pending		
Pharm/Tox	Pending		
Biopharm	Acceptable	September 23, 2003	Andre Jackson, Ph.D.
LNC	USAN available	NA	
Methods Validation	Pending		
OPDRA	Pending		
EA	Acceptable, categorical exclusion granted as per information from Sepracor	As per this review	Gurpreet Gill-Sangha, Ph.D.
Microbiology	NA		

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Executive Summary Section

Scotia, Canada. The packaging and testing is also performed at the — or Sepracor sites. The DMF's for (RS)-zopiclone were reviewed and found deficient by Dr. Gurpreet Gill-Sangha and deficiency letters were sent to all three DMF suppliers. Sepracor has provided stability data for 24 months. The deficiencies in the drug substance section are related to additional information on manufacture of eszopiclone, specifications for raw materials and intermediates and drug substance for impurities — and stability protocol for future batches of eszopiclone.

The drug product, Estorra tablets, is formulated as film coated tablets for oral administration in the 2 and 3 mg strengths. The — contains active eszopiclone with microcrystalline cellulose, — calcium phosphate, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate which are all either NF or USP technical grade.

— olue for the — 3 mg tablets, respectively. The commercial batch size may range up to — Estorra tablets are manufactured, packaged and tested by the contractor Pantheon Inc., Mississauga, Ontario, Canada. The tablets are manufactured by the — film coat. Primary stability data include — for — 2 mg batches and — for — 3 mg batches in — bottles for commercial packs. In addition, — accelerated data was provided for samples in bottles. ambient and — accelerated data was provided for — 2 mg batches in

Impurities — were not monitored during release and stability. Other deficiencies in the drug product section relate to additional information on manufacturing, overages, impurities and microbial specifications at release and on stability. Changes in the description section of package insert and storage statement for container and carton labels are recommended.

Four different strengths 1, 1.5, 2 and 3 mg were used for the purpose of investigational formulations. The 2 and 3 mg formulations are identical to the proposed commercial product and the 1 and 1.5 are essentially identical to the proposed 2 mg commercial product with : — .0 offset the incremental difference in active ingredient. In addition to the tablet formulations, oral solution formulations were used in some clinical studies consisting of aqueous solutions of eszopiclone and sodium phosphate buffer. Except for the change from oral solution to tablet formulations, no other formulation changes occurred during development.

## Executive Summary Section

**B. Description of How the Drug Product is Intended to be Used**

The recommended dose for Estorra tablets is  $\frac{1}{2}$  daily before bedtime. The dose is  $\frac{1}{4}$  for the elderly and patients with severe hepatic impairment. The total daily dose should not exceed 3 mg. Estorra is intended for the treatment of insomnia characterized by difficulty falling asleep, and/or difficulty maintaining sleep during the night and early morning. Estorra is proposed to decrease sleep latency and improve sleep maintenance. Estorra is packaged in  $\frac{1}{2}$  bottles in 100 count per bottle and  $\frac{1}{2}$ . The storage condition is at 25 °C (77 °F) with excursions permitted to 15° to 30 °C (59 to 86 °F).

**C. Basis for Approvability or Not-Approval Recommendation**

NDA 21-476 for Estorra (eszopiclone) tablets is recommended **APPROVABLE** from the CMC standpoint based on the following:

- ◆ Pending recommendation from FDA Compliance regarding cGMP status of manufacturing, packaging, controls and testing facilities.
- ◆ Adequate responses to CMC concerns related to the drug substance and drug product sections as listed on pages 96-98 of this review.

**III. Administrative**

Reviewer – Gurpreet Gill-Sangha, Ph.D.  
Chemistry Team Leader – Thomas Oliver, Ph.D.  
Project Manager – Merrill Mille, R.Ph.

85 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

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

/s/

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Gurpreet Gill-Sangha  
9/29/03 04:27:47 PM  
CHEMIST

CMC review 1 for NDA 21-476

Thomas Oliver  
9/30/03 10:09:56 AM  
CHEMIST