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

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List of Tables

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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:

Previous Documents	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
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:

Submission(s) Reviewed	Document Date
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

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

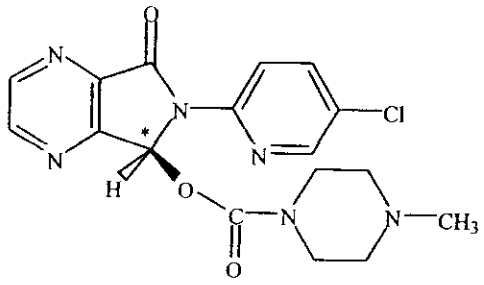
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____ SPOTS product – Form Completed
    ___X___ 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:	(+)-(5*S*)-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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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

[1] 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")
[2] 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	

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
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

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 for **APPROVAL** from the CMC standpoint. The approval from the CMC standpoint is based on an overall acceptable cGMP recommendation from FDA Compliance for all the manufacturing, packaging and testing sites and adequate responses to CMC deficiencies from Chemistry review #1 as evaluated in this review.

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 1, 2 and 3 mg strengths ir — — bottles containing 100 dosage units per bottle.

—

. The 3 mg tablet is round, blue film-coated, the 2 mg tablet is round, white film-coated and the 1 mg tablet is round, light blue 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, and —). A — 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 — (DMF — , — (DMF — and — (DMF — Eszopiclone drug substance is manufactured from

(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 s 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 ablets). 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 ottles and Based on of stability data provided for commercial light blue 1 mg strength and supportive data for i mg strength, a 15 month expiry is granted for 1 mg in bottles. At the time of this review, no information about 1 mg s 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

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 for 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.

45 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Gurpreet Gill-Sangha
11/29/04 04:30:47 PM
CHEMIST
Recommend AP
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

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):

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

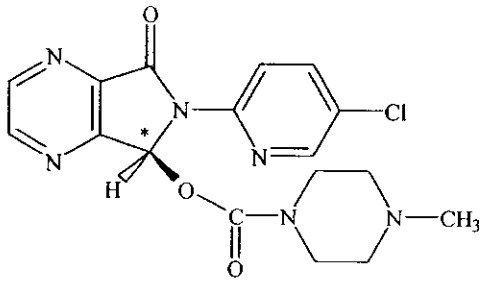
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
___X___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:	(+)-(5*S*)-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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Refer to Chemistry Review #1

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	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	
	III			4	Adequate	See CMC review #1	

Executive Summary Section

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	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	

[1] 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")

[2] 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	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.

— he 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, —. A — form of eszopiclone (molecular weight 388.81) was found by — using — — he particle size of eszopiclone is between —. (RS)-zopiclone is purchased from any of the three suppliers which are — a (DMF — (DMF — and — (DMF —). Eszopiclone drug substance is manufactured from (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 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 i' ¯_ 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 – Merril 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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/s/

Gurpreet Gill-Sangha
11/6/03 03:06:54 PM
CHEMIST

CMC Review 2 for NDA 21-476

Thomas Oliver
11/6/03 03:12:53 PM
CHEMIST

NDA 21-476

Estorra™ (Eszopiclone)

Sepracor Inc.

Gurpreet Gill-Sangha, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

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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):

- 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

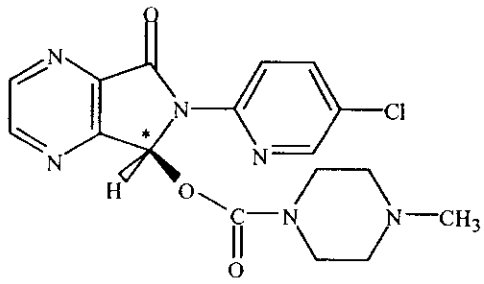
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed
__X___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:	(+)-(5*S*)-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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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—	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	
—	III			4	Adequate	As per this review	

Executive Summary Section

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	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	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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	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		

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 pending acceptable cGMP recommendation from FDA Compliance for all the manufacturing, packaging and testing sites and adequate responses to CMC deficiencies as noted in this review.

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, — A — — form of eszopiclone (molecular weight 388.81) was found by — — The particle size of eszopiclone is between (RS)-zopiclone is purchased from any of the three suppliers which are — (DMF , — (DMF — and — DMF — Eszopiclone drug substance is manufactured from (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 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 techincal 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 : — 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 and — . 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 – Merril Mille, R.Ph.

85 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

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