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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**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS**

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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
   BC Amendment                                November 24, 2004
   E-mail

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: I
      • 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):
    __X__ 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_{6}O_{3}

   Molecular Weight: 388.81

   CAS registry #: 138729-47-2

   Structure:

   ![Chemical Structure](image)

   * = Chiral center
17. RELATED/SUPPORTING DOCUMENTS:

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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

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## Chemistry Assessment Section

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<td>As per this review for all strengths (1, 2 and 3 mg)</td>
<td>Gurpreet Gill-Sangha, Ph.D.</td>
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<td>November 23, 2004</td>
<td>James McVey, Ph.D.</td>
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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 in 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

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 and (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 DMP’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 stability data provided for commercial light blue 1 mg strength and supportive data for 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
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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
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VII. ESTABLISHMENT INSPECTION ...........................................................................11

VIII. DRAFT DEFICIENCY LETTER .................................................................................20
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

6. SUBMISSION(S) BEING REVIEWED:

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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: (+)-(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_{6}O_{3}
   Molecular Weight: 388.81
   CAS registry #: 138729-47-2
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   * = Chiral center
### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs: Refer to Chemistry Review #1

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### CHEMISTRY REVIEW

Executive Summary Section

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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, 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 a (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. The tablets may range up to 3 mg tablets, respectively. The commercial batch size

do not exceed 5,000 tablets. 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 – Merril Mille, R.Ph.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS.........1

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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

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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):
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: (+)-(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_{6}O_{3}

Molecular Weight: 388.81

CAS registry #: 138729-47-2

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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 and DMF. Eszopiclone drug substance is manufactured from (RS)-zopiclone at either the or the Sepcor site at Nova
Scotia, Canada. The packaging and testing is also performed at the 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 zopiclone, specifications for raw materials and intermediates and drug substance for impurities and stability protocol for future batches of zopiclone.

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

Tablet blue for the 3 mg tablets, respectively. The commercial batch size may range up to 100 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 zopiclone 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 10 mg daily before bedtime. The dose is reduced 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 100 count bottles in bottles in 100 count per bottle and bottles in 100 count per bottle and bottles in 100 count per bottle and 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 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
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