CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200603

CHEMISTRY REVIEW(S)

NDA 200-603

LATUDA (Lurasidone Hydrochloride) Tablets, 40 mg and 80 mg

Sunovion Pharmaceuticals, Inc.

Division of Psychiatry Products, HFD 130

Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Received Date: 30-DEC-2009
PDUFA Goal Date: 30-OCT-2010

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-603

2. REVIEW #: 2

3. REVIEW DATE:26-OCT-2010

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 200-603 Original Submission	30-DEC-2009
NDA 200-603 Amendment (SD #6)	04-MAR-2010
NDA 200-603 Amendment (SD#17)	27-MAY-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 200-603 Amendment (SD#34)	17-SEPT-2010
NDA 200-603 Amendment (SD#37)	07-OCT-2010
NDA 200-603 Amendment (SD#40)	13-O8T-2010
NDA 200-603 Amendment (SD#43)	18-OCT-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Sunovion Pharmaceuticals Inc.
Address:	One Bridge Plaza, Suite 510 Fort Lee, NJ 07024
Representative:	Bridget Walton Director, Regulatory Affairs Sunovion Pharmaceuticals Inc.
Telephone:	(201) 228-8333

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LURASIDONE
b) Non-Proprietary Name (USAN): Lurasidone Hydrochloride
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50 , 505(b)(1)

10. PHARMACOL. CATEGORY: Psychiatry, Schizophrenia

11. DOSAGE FORM: Immediate Release Tablets

12. STRENGTH/POTENCY: 40 mg and 80 mg tablets

13. ROUTE OF ADMINISTRATION: Oral

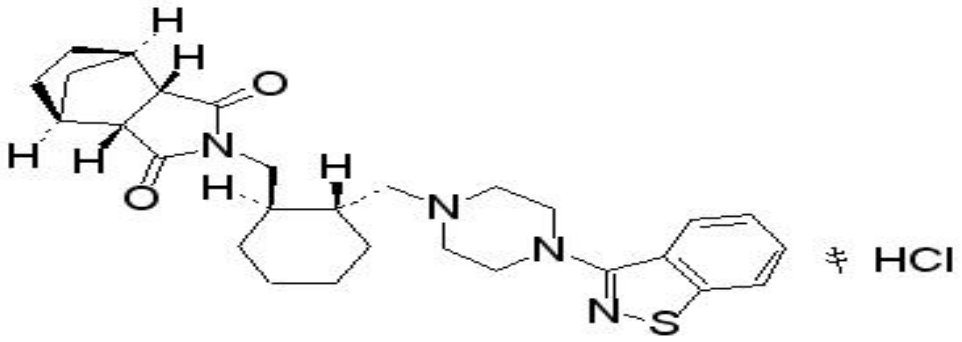
14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

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:

Chemical Names:	(3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano -2*H*isoindole-1,3-dione hydrochloride
Molecular Formula:	$C_{28}H_{36}N_4O_2S$. HCl
Molecular Weight:	492.68 Lurasidone free base 529.14 Lurasidone Hydrochloride salt
CAS:	[367514-88-3]



Note: The chemical structure presented in Review #1 was replaced with this structure included in labeling

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16059	II	Dainippon Sumitomo Pharma	Drug substance	1	Adequate	Aug-27-2010	Reviewed by S. Bhamidipati
(b) (4)	IV		(b) (4)	4	Adequate*		
	III			3,4	Adequate*		
	III			3,4	Adequate*		
	III			3,4	Adequate*		
	III			3,4	Adequate*		
	IV			3,4	Adequate*		
	III			3,4	Adequate*		
	III			3,4	Adequate*		Last reviewed 03-Apr-2005
	III			4	Adequate*		
	III			4	Adequate*		
	III			3,4	Adequate*		Last reviewed 01-Aug-2006
	III			3	Adequate*		Last reviewed 31-Dec-2008
	III			3,4	Adequate*		Last reviewed 7-Jan-2004
	III			3,4	Adequate*		Last reviewed 06-Feb-2008
	III			4	Adequate*		

[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")
* Solid Oral Dosage form
[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61292	Lurasidone Hydrochloride tablets

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Not applicable		
EES	Overall Acceptable	26-OCT-2010	E. Johnson
Pharm/Tox	Approval recommended	19-OCT-2010 20-OCT-2010	Sonia Tabocova, Ph.D. Aisar Atrkachi, Ph.D.
Biopharmaceutics	Approval recommended	27-OCT-2010	Houda Mahayni, Ph.D.
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Sponsor proposed trade name Latuda was considered acceptable.	21-OCT-2010	Richard Abate, RPh.
EA	Waiver granted		
Microbiology	Not applicable as this is a solid oral dosage form		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 200-603

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

This NDA for Latuda (Lurasidone Hydrochloride) Tablets (40, and 80 mg) for treatment of Schizophrenia is recommended for approval from CMC perspective. However, it should be noted that the clinical division is not approving the 120 mg strength tablets. The proposed acceptance criteria for dissolution testing (Q_{30} NLT (b) (4)) of the drug product are considered not appropriate and the acceptance criterion for dissolution testing should meet (b) (4) at 20 minutes. This information was communicated to the applicant and the sponsor accepted was accepted the change. The proposed 30 month expiration dating for the drug product is supported by the stability data submitted by the sponsor. The Office of Compliance has provided an overall acceptable recommendation for the manufacturing and the testing facilities. The proposed trade name, Latuda for the drug product was considered acceptable by Division of Medication Error and Prevention Analysis. The changes in labeling from CMC perspective were also captured at the end of this review.

Notes: This review is an evaluation of sponsor provided response to the IR letter (dated 20-Aug-2010). Please refer to the review finalized in DARRTS (dated 27-Aug-2010) for comprehensive CMC evaluation of this NDA. This NDA was originally submitted by Dainippon Sumitomo Pharma America, Inc,. and the rights were transferred to Sepracor, Inc. during the course of review process. The name of Sepracor, Inc. was recently changed to Sunovion Pharmaceutical Inc.

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

Not included in this review.

II. Summary of Chemistry Assessments

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

Drug Product:

The proposed drug product, Lurasidone consists of the active Lurasidone Hydrochloride, an antipsychotropic compound and a new molecular entity in the chemical class of benzoisothiazole derivatives. Lurasidone Hydrochloride was developed by Dainippon Sumitomo Pharma in collaboration with Merck Research Laboratories (during the initial IND stages) for treatment of Schizophrenia. Lurasidone Hydrochloride formulations designated Group A and B were used in clinical studies in Japan, Europe and US whereas Group C formulation were developed solely for the purpose of commercialization. The

drug product is offered in 40, 80 and 120 mg strengths and each strength is film-coated with non-functional but acceptable colors that comply with CFR for use in foods and drugs. The drug product is either round shaped biconvex (for 40 mg strength) or oval shaped film coated tablet (for 80 (b) (4) mg strengths) with white film-coating (pale green color coat for 80 mg strength) and strength identifying debossing of markings of L40, L80 and (b) (4) The commercial formulation contains common pharmaceutical excipients, mannitol, pregelatinized starch, hydroxy propyl methyl cellulose (b) (4), croscarmellose, magnesium stearate in a dose proportional quantitative composition. The drug product will be available as 30 , 90 and 500 count tablets packaged in a (b) (4) container with (b) (4) child resistant closure with induction seal liner and push thru alu-foil blister strips containing 7 or 10 tablets of a given dosage strength.

(b) (4)

(b) (4) A set of six batches of lowest (40 mg) and (b) (4) Lurasidone tablets manufactured at development scale without debossing and packaged in different configurations and stored at long term storage conditions of 25C/60%RH were evaluated for appearance, assay, organic impurities, dissolution and (b) (4) for stability per ICH guidelines. Stability data obtained were statistically assessed for pooling of batches within each set of packaging configuration and linear regression analysis was employed for estimation of expiration date. In addition, stability data obtained for Lurasidone tablets manufactured at the commercial scale (and the facility) for three batches of each strength and packaged as intended for marketing were provided up to 6 months. The drug product is recommended to be stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature).

Drug Substance:

Lurasidone hydrochloride (Lurasidone HCl) drug substance is a white to off-white crystalline powder (b) (4) the chemical structure of lurasidone HCl (including the absolute configuration) was determined to be (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2*H*isoindole-

1,3-dione hydrochloride . Lurasidone HCl has an aqueous solubility of 0.224 mg/mL in water with maximum solubility of 0.349 mg/mL in pH 3.5 buffer. Lurasidone Hydrochloride, is manufactured by Dainippon Sumitomo Pharma at their Oita plant in Japan and the sponsor referred to DMF #16059 through a letter of authorization from the DMF holder. The DMF was reviewed and found adequate following DMF holder provided response to the deficiencies identified in the initial review. The drug substance is stable for 36 months when stored at 25°C/60% RH and adequately tested at the drug product manufacturing site prior to use.

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

Latuda (Lurasidone Hydrochloride) tablets of 40 and 80 mg strength will be supplied as 30 , 90 and 500 count units packaged in a (b) (4) container with child resistant (b) (4) (with induction seal liner)and individual push thru alu-foil blisters (7 or 10 count strips). Latuda will be administered on once a day schedule, with food, generally beginning with 40 mg. The maximum recommended dose is 80 mg once daily. The recommended storage conditions for the drug product are: "Store at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature)."

C. Basis for Approvability or Not-Approval Recommendation

This NDA for Latuda (Lurasidone Hydrochloride) Tablets (40, and 80 mg) is recommended for approval from CMC perspective. A shelf-life of 30 months is recommended for expiration dating of the product based on stability data submitted. The acceptance criterion for dissolution was changed from Q_{30} NLT (b) (4) to Q_{20} NLT (b) (4) based on evaluation of data submitted and in collaboration with Biopharmaceutical reviewer. The Office of Compliance has provided an overall acceptable recommendation for the manufacturing and the testing facilities.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D.
CMC Lead Name/T. Chhagan
Project Manager Name: Ann J. Sohn

C. CC Block

Original NDA 200-603
DPP(HFD-130)/CSO/A. Sohn
ONDQA/ DNDQAI /PAL/T. Chhagan
ONDQA/DNDQAI /Brach Chief/R. Sood
DPP (HFD-130)/NDA Division File
ONDQA/DNDQAI/Chemist/S. Bhamidipati
ONDQA/DNDQAI RPM/T. Bouie

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/s/

SHASTRI P BHAMIDIPATI
10/27/2010

RAMESH K SOOD
10/27/2010

ONDQA Division Director's Memo
NDA 200-603, LATUDA (lurasidone hydrochloride) tablets
40 mg and 80 mg (strengths correspond to the HCl salt)
Date: 26-OCT-2010

Introduction

Latuda (lurasidone hydrochloride) immediate release tablets are for the treatment of schizophrenia. **The strengths of this drug product should have been expressed as the neutral species to be in keeping with ONDQA and USP drug product established name nomenclature practices and policies.**
ONDQA recommends approval of this NDA.

Administrative

The original submission of this 505(b)(1) NDA was received 30-DEC-2009 from Sepracor, Inc., of Fort Lee, NJ. The drug substance is a new molecular entity (NME). Two CMC amendments were received on 04-MAY-2010 and 27-MAY-2010 and reviewed.

This NDA is supported by IND 61292 and sixteen DMF's. The consult for the PAI (EES) was found to be overall acceptable as of today.

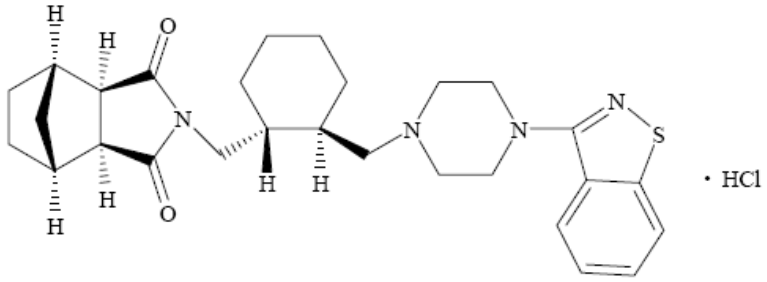
ONDQA recommends approval from the Chemistry, Manufacturing and Controls perspective.

Drug Substance (lurasidone hydrochloride)

The full chemical name for the drug substance (USAN) is: (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4- (1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2*H*isoindole-1,3-dione hydrochloride

Molecular Formula: $C_{28}H_{36}N_4O_2S.HCl$
Molecular Weight: 492.68 Lurasidone base
529.14 Lurasidone Hydrochloride salt
CAS: [367514-88-3]

Chemical structure



Lurasidone hydrochloride drug substance is a white to off-white crystalline powder and consists of six chiral centers. The drug substance is obtained in only one crystalline form. The absolute stereochemistry is confirmed.

Lurasidone Hydrochloride, is manufactured by Dainippon Sumitomo Pharma at their Oita plant in Japan (DMF 16059). The DMF was reviewed and found adequate after the DMF Holder provided adequate responses to deficiencies. The drug substance is adequately tested at the drug product manufacturing site.

Lurasidone hydrochloride has an aqueous solubility of 0.224 mg/mL in water with maximum solubility of 0.349 mg/mL in pH 3.5 buffer.

The approved drug substance retest interval is (b) (4)**.**

Drug Product (immediate release tablets).

The drug product is supplied as immediate release tablets. Strengths corresponding to 40 mg, 80 mg, and 120 mg of lurasidone hydrochloride were developed. For clinical reasons, the 120 mg strength will not be approved. **The strength of this drug product should have been expressed as the neutral species to be in keeping with ONDQA and USP drug product established name nomenclature practices and policies.**

The commercial formulation contains common pharmaceutical excipients, mannitol, pregelatinized starch, hydroxypropylmethyl cellulose (b) (4), croscarmellose, magnesium stearate in a **dose proportional** composition.

The manufacturing process consists of (b) (4) with magnesium stearate and strength specific color film color and tablet shape as follows:

40 mg strength white film coated round tablets
80 mg strength pale green film coated oval tablets.

The drug product will be supplied as 30 , 90 and 500 count tablets packaged in a (b) (4) plastic container with (b) (4) child resistant closure with induction seal liner and push thru aluminum-foil blister strips containing 7 or 10 tablets of a given strength. A dissolution specification of not less than (b) (4) in 20 minutes is recommended to be approved.

The drug product is to be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) A thirty (30) month drug product expiry is approved for both strengths in both bottle and blister package presentations.
ONDQA recommends approval of this NDA from the CMC perspective.

Rik Lostritto, Director, ONDQA Division I

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

/s/

RICHARD T LOSTRITTO
10/26/2010

NDA 200-603

Lurasidone (Lurasidone Hydrochloride) Tablets, 40 mg, 80 mg and 120 mg

Sepracor, Inc.

Division of Psychiatry Products, HFD 130

Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Received Date: 30-DEC-2009
PDUFA Goal Date: 30-OCT-2010

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-603

2. REVIEW #: 1

3. REVIEW DATE: 1-AUGUST-2010

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 200-603 Original Submission	30-DEC-2009
NDA 200-603 Amendment (SD #6)	04-MAR-2010
NDA 200-603 Amendment (SD#17)	27-MAY-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Sepracor Inc.
Address:	One Bridge Plaza, Suite 510 Fort Lee, NJ 07024
Representative:	Bridget Walton Director, Regulatory Affairs Sepracor Inc.
Telephone:	(201) 228-8333

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LURASIDONE
b) Non-Proprietary Name (USAN): Lurasidone Hydrochloride
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50 , 505(b)(1)

10. PHARMACOL. CATEGORY: Psychiatry, Schizophrenia

11. DOSAGE FORM: Immediate Release Tablets

12. STRENGTH/POTENCY: 40 mg, 80 mg and 120 mg tablets

13. ROUTE OF ADMINISTRATION: Oral

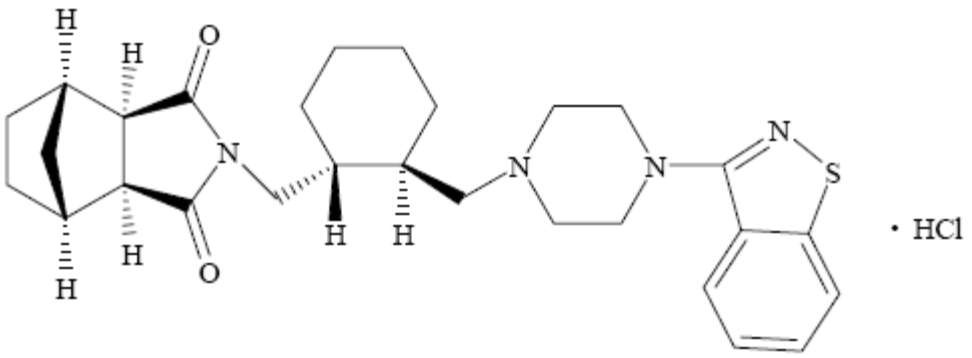
14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

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:

Chemical Names:	(3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4- (1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano -2*H*isoindole-1,3-dione hydrochloride
Molecular Formula:	$C_{28}H_{36}N_4O_2S$. HCl
Molecular Weight:	492.68 Lurasidone free base 529.14 Lurasidone Hydrochloride salt
CAS:	[367514-88-3]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16059	II	Dainippon Sumitomo Pharma	Drug substance	1	Adequate	Aug-27-2010	Reviewed by S. Bhamidipati
(b) (4)	IV		(b) (4)	4	Adequate*		
	III			3,4	Adequate*		
	III			3,4	Adequate*		
	III			3,4	Adequate*		
	III			3,4	Adequate*		
	IV			3,4	Adequate*		
	III			3,4	Adequate*		
	III			3,4	Adequate*		Last reviewed 03-Apr-2005
	III			4	Adequate*		
	III			4	Adequate*		
	III			3,4	Adequate*		Last reviewed 01-Aug-2006
	III			3	Adequate*		Last reviewed 31-Dec-2008
	III			3,4	Adequate*		Last reviewed 7-Jan-2004
	III			3,4	Adequate*		Last reviewed 06-Feb-2008
	III			4	Adequate*		

[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")
* Solid Oral Dosage form
[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61292	Lurasidone Hydrochloride tablets

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Not applicable		
EES	OC recommendation pending		
Pharm/Tox	Not applicable		
Biopharmaceutics	Review pending		Dr. Houda Mahayni
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Proposed trade name was not acceptable		
EA	Waiver granted		
Microbiology	Not applicable as this is a solid oral dosage form		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 200-603

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

This NDA for Lurasidone Tablets (40, 80 and 120 mg) is approvable from CMC perspective pending satisfactory responses from the sponsor to the issues identified at the end of this review. The proposed acceptance criteria for dissolution testing (Q_{30} NLT (b) (4) of the drug product are considered not appropriate and a final recommendation by Biopharmaceutical Reviewer is pending. The proposed 30 month expiration dating for the drug product is supported by the stability data submitted by the sponsor. However, any changes in dissolution acceptance criteria as recommended by Biopharmaceutical Reviewer would also require further evaluation of stability data supporting the expiration dating. Additionally, Office of Compliance has not provided a final recommendation as to the acceptability of manufacturing and testing facilities for the drug product. It should also be noted that this review does not include any labeling changes from CMC perspective since the trade names (b) (4)) proposed by the sponsor were not considered as acceptable by Division of Medication Error and Prevention Analysis.
Note: This NDA was originally submitted by Dainippon SumitomoPharma America, Inc,. and the rights were transferred to Sepracor, In. during the course of review process.

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

Not included in this review.

II. Summary of Chemistry Assessments

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

Drug Product:
The proposed drug product, Lurasidone consists of the active Lurasidone Hydrochloride, an antipsychotropic compound and a new molecular entity in the chemical class of benzoisothiazole derivatives. Lurasidone Hydrochloride was developed by Dainippon Sumitomo Pharma in collaboration with Merck Research Laboratories during the initial IND stages and was formulated as a tablet for conducting the clinical studies in US. Lurasidone Hydrochloride formulations designated Group A and B were used in clinical studies in Japan, Europe and US whereas Group C formulation were developed solely for the purpose of commercialization. The drug product is offered in 40, 80 and 120 mg strengths and each strength is film-coated with non-functional but acceptable colors that comply with CFR for use in foods and drugs. The drug product is either round shaped biconvex (for 40 mg strength) or oval shaped film coated tablet (for 80 and (b) (4)

strengths) with white film-coating (pale green color coat for 80 mg strength) and strength identifying debossing of markings of L40, L80 (b) (4). The commercial formulation contains common pharmaceutical excipients, mannitol, pregelatinized starch, hydroxy propyl methyl cellulose (b) (4), croscarmellose, magnesium stearate in a dose proportional quantitative composition. The drug product will be available as 30 , 90 and 500 count tablets packaged in a (b) (4) plastic container with (b) (4) child resistant closure with induction seal liner and push thru alu-foil blister strips containing 7 or 10 tablets of a given dosage strength.

(b) (4)

(b) (4) Lurasidone tablets manufactured at development scale without debossing and packaged in different configurations and stored at long term storage conditions of 25C/60%RH were evaluated for appearance, assay, organic impurities, dissolution and (b) (4) for stability per ICH guideline. Stability data obtained were statistically assessed for pooling of batches within each set of packaging configuration and linear regression analysis was employed for estimation of expiration date. In addition, stability data obtained for Lurasidone tablets manufactured at the commercial scale (and the facility) for three batches of each strength and packaged as intended for marketing were provided up to 6 months. The drug product is recommended to be stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature).

Drug Substance:

Lurasidone hydrochloride (Lurasidone HCl) drug substance is a white to off-white crystalline powder (b) (4) the chemical structure of lurasidone HCl (including the absolute configuration) was determined to be (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2*H*isoindole-1,3-dione hydrochloride . Lurasidone HCl has an aqueous solubility of 0.224 mg/mL in water with maximum solubility of 0.349 mg/mL in pH 3.5 buffer. Lurasidone

Hydrochloride, is manufactured by Dainippon Sumitomo Pharma at their Oita plant in Japan and the sponsor referred to DMF #16059 through a letter of authorization from the DMF holder. The DMF was reviewed and found adequate following DMF holder provided response to the deficiencies identified in the initial review. The drug substance is adequately tested at the drug product manufacturing site prior to use.

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

LURASIDONE (Lurasidone Hydrochloride) tablets will be supplied as 30 , 90 and 500 count units packaged in a (b) (4) plastic container with child resistant (b) (4) closure (with induction seal liner)and individual push thru alu-foil blisters (7 or 10 count strips). LURASIDONE is administered on a once a day schedule, with food, generally beginning with 40 mg or 80 mg initially The maximum recommended dose is 120 mg once daily. The recommended storage conditions for the drug product are: "Store at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature)."

C. Basis for Approvability or Not-Approval Recommendation

This NDA for LURASIDONE (Lurasidone Hydrochloride) Tablets (40, 80 and 120 mg) is approvable from CMC perspective pending satisfactory responses from the sponsor to the deficiencies identified at the end of this review. A shelf-life of 30 months is recommended for expiration dating of the product based on stability data submitted. However, it should be noted that any changes in the dissolution method and the acceptance criteria would require complete evaluation of any new data submitted in this regard. Additionally, the Office of Compliance has not provided an overall recommendation for the manufacturing and the testing facilities at the time of completing this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D.
CMC Lead Name/Date: Thomas Oliver
Project Manager Name: Ann J. Sohn

C. CC Block

Original NDA 200-603
DPP (HFD-130)/NDA Division File
DPP(HFD-130)/CSO/A. Sohn
ONDQA/DNDQAI/Chemist/S. Bhamidipati
ONDQA/ DNDQAI /PAL/T. Oliver
ONDQA/DNDQAI RPM/T. Bouie
ONDQA/DNDQAI /Brach Chief/R. Sood

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200603	ORIG-1	SEPRACOR INC	Lurasidone HCl

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/s/

SHASTRI P BHAMIDIPATI
08/27/2010

RAMESH K SOOD
08/27/2010

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 200-603	**Supplement Number and Type: Original**	**Established/Proper Name: (b) (4)(Lurasidone) tablets**
Applicant: Dainippon Sumitomo Pharma America	**Letter Date:30-Dec-2009**	**Stamp Date: 30-Dec-2009**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?		x	Facilities lists were provided in at the appropriate sections of Module 3 (3.S.2 and 3.P.2)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			Not Applicable

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		X	
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

PRODUCT QUALITY (Small Molecule)
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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Answers to Questions 12-18 are based on information contained within DMF
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

PRODUCT QUALITY (Small Molecule)
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E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	The sponsor claims to have developed DP through the use of QTTP, CQAs and DoEs.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Not applicable

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
16059	II	DSP	Drug substance	28-Dec-2009	
(b) (4)	IV		(b) (4)	24-Apr-2006	
	III			09-May-2008	
	III			28-Oct-2008	
	III			21-Apr-2009	
	III			21-Apr-2009	
	IV			24-Aug-2009	
	III			2-Sep-2009	
	III			9-May-2008	
	III			9-May-2008	
	III			5-Nov-2009	
	III			25-Aug-2009	
	III			31-Dec-2008	
	III				
	III			19-Aug-2009	
	III			28-Jul-2009	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not Applicable
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			Not Applicable

{See appended electronic signature page}

Name of
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

{See appended electronic signature page}

Name of
Branch Chief Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200603	ORIG-1	DAINIPPON SUMITOMO PHARMA AMERICA INC	Lurasidone HCl

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/s/

SHASTRI P BHAMIDIPATI
02/25/2010

RAMESH K SOOD
02/25/2010

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**200603**
Applicant:	Dainippon Sumitomo Pharma America, Inc.
Letter Date:	30-DEC-09
Stamp Date:	30-DEC-09
PDUFA Date:	30-OCT-10
Trademark:	(b) (4)
Established Name:	lurasidone hydrochloride
Dosage Form:	Tablets (40, 80, and 120 mg)
Route of Administration:	Oral
Indication:	**S**chizophrenia
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary

Lurasidone is indicated for the acute treatment of adult patients with schizophrenia and was developed under IND 61,292 (Dainippon Sumitomo Pharma America). Lurasidone HCl is an antipsychotic of the benzisothiazole derivative class. In vitro receptor binding studies revealed that lurasidone is an antagonist with high affinity at dopamine D_2 receptors and the 5-hydroxytryptamine (5-HT, serotonin) receptors, $5\text{-}HT_{2A}$ and $5\text{-}HT_7$; is an antagonist with moderate affinity at human α_{2C} adrenoceptors; is a partial agonist at serotonin $5\text{-}HT_{1A}$ receptors; and is an antagonists at α_{2A} adrenoceptors. The applicant had a CMC EOP2 meeting (September 19, 2002) where the following issues were discussed: starting material designation and drug substance stability data. The applicant had a CMC pre-NDA meeting (February 19, 2009) where the following CMC issues were discussed: drug substance specifications, chloride content method, drug product specifications, and the drug product stability program. Minutes for both meetings can be found in DARTS and should be read by the reviewer.

Drug Substance

Lurasidone HCl is a white to off-white powder. (b) (4) Solubility in water is 0.224 mg/mL (20 C). The drug substance will be manufactured by Dainippon Sumitomo Pharma Co., Ltd. (Oita, Japan). The NDA applicant references DMF #16059 (Dainippon Sumitomo Pharma Co., Ltd.) for information on lurasidone HCl (LoA 10-DEC-09). DMF #16059 was submitted 15-JUL-01. The DMF was reviewed (Dr. Sherita McLamore, 16-OCT-09) to answer specific CMC questions but was not reviewed as part of a formal IND or NDA review. Lurasidone HCl drug substance is stored in (b) (4) (b) (4)

Drug Product

(b) (4) (lurasidone HCl) tablets will be available in 40, 80, and 120 mg strengths. The recommended starting and target dose of (b) (4) is 40 mg or 80 mg once daily. Initial dose titration is not required. Labeling states that (b) (4) has been shown to be (b) (4) Some patients may benefit from

(b) (4)

tablets are film coated tablets which differ in color, size, shape and debossing. The core tablets of the three strengths are proportional in composition. The only difference is the addition of (b) (4) (b) (4). The sponsor developed 20, 40, 80, (b) (4) The tablet cores are comprised of: lurasidone HCl, mannitol, pregelantized starch, croscarmellose sodium, hypromellose, and magnesium stearate. The film coat is comprised of: Opadry (b) (4), yellow ferric oxide (b) (4) FD&C Blue No. 2 Aluminum Lake (b) (4) and carnauba wax. The drug product will be manufactured by (b) (4)

. The blisters will be aluminum induction seal or push-through aluminum/ aluminum unit-dose blisters. The applicant has requested a (b) (4) expiry for lurasidone HCl tablets

<u>Critical Issues for Review</u>

• The NDA applicant references DMF #16059 (Dainippon Sumitomo Pharma Co., Ltd.) for information on lurasidone HCl (LoA 10-DEC-09). DMF #16059 was submitted 15-JUL-01 and was reviewed (Dr. Sherita McLamore, 16-OCT-09) to answer specific CMC questions but was not reviewed as part of a formal IND or NDA review. DMF #16059 will need to be reviewed and found acceptable.

• (b) (4)

• The compatibility of the drug product excipients will need to be evaluated.

• The applicant has developed a number of drug product formulations (pre-A, A, B, C, MRL Group A, MRL Group C, MRL Group D, MRL Group E) throughout development. Most phase-II and all phase-III studies utilized drug product formulation B. The commercial formulation is C. It is unknown why the formulation was changed (i.e., to correct a problem). It will need to be determined whether formulation C was studied clinically and how different it is from the clinically studied formulations (e.g., B).

• The differences in the manufacturing process from the proposed commercial process to that of the processes used to generate clinically studied drug product lots will need to be evaluated. The performance of the commercial product will need to be linked to the performance of the clinically studied product (e.g., formulation, manufacturing process, packaging).

• (b) (4)

• (b) (4)

• (b) (4) tablets are differentiated by the use of color, size, shape, and debossing [40 mg: white to off-white, round film-coated tablet, debossed with “L 40”; 80 mg: pale green, oval film-coated tablet, debossed with “L 80”; (b) (4) . Samples will need to be requested and the acceptability of the appearance specification will need to be evaluated.

• Microbial limits testing is proposed as a “sunset provision”, to be performed for release and stability testing of the first three commercial batches and removed thereafter. The acceptability of the applicant’s strategy will need to be determined.

• No water content testing is performed at release. The acceptability of not testing for water content will need to be determined.

• (b) (4)

- (b) (4)

- (b) (4)
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- (b) (4)

• The applicant has proposed an expiry of (b) (4). The applicant has submitted three sets (S-1, S-2, and S-3) of stability data to support the expiry.

• It appears the dose strengths (40, 80, and 120 mg lurasidone HCl) are correctly labeled as 40, 80, and 120 mg in the lurasidone HCl label. Reviewer will need to confirm.

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. My recommendation would be for a single reviewer to be assigned to the NDA. As Dr. Sherita McLamore was involved in the previous CMC meetings, she would be the recommended reviewer. It will be important for the assigned reviewer to open all links found in the CMC sections of the electronic NDA, as a lot of historical data and justification for various approaches are contained there. The applicant claims a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(b) as the expected introduction concentration (EIC) of lurasidone in the aquatic environment is below 1 parts per billion and states that to the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment. The manufacturing, testing, and packaging sites will need to be submitted into EES (by the ONDQA PM), however, the reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200603	ORIG-1	DAINIPPON SUMITOMO PHARMA AMERICA INC	Lurasidone HCl

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/s/

THOMAS F OLIVER
01/25/2010

RAMESH K SOOD
01/25/2010