

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-173

CHEMISTRY REVIEW(S)

NDA 22-173

**Zyprexa[®] TRADENAME
(Olanzapine) for extended-release injectable suspension
210, 300, 405 mg/vial**

**Review#3
Sponsor's Response to IR letter**

Eli Lilly and Company

David J. Claffey Ph.D

**Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment**

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-173
2. REVIEW #: 3
3. REVIEW DATE: 15 October 2008
4. REVIEWER: David J. Claffey, PhD.

5. PREVIOUS DOCUMENTS:

Previous Documents

NDA 22-173
NDA 22-173 Response (CMC)

Document Date

30-Apr-2007
30-Jan-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA 22-173 amendment

Document Date

13-Jun-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Eli Lilly and Company
Address: Lilly Corporate Center, Indianapolis, IN 46285
Representative: Robin Pitts Wojcieszek, R.Ph., Associate Director,
U.S. Regulatory Affairs
Telephone: (317) 651-9827

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: Zyprexa[®] TRADENAME
b) Non-Proprietary Name (USAN): Olanzapine For Injectable Suspension
c) Code Name/# (ONDC only): LY170053
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 2
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of Schizophrenia

11. DOSAGE FORM: For Injectable Suspension

12. STRENGTH/POTENCY: 210, 300, 405 mg/vial

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

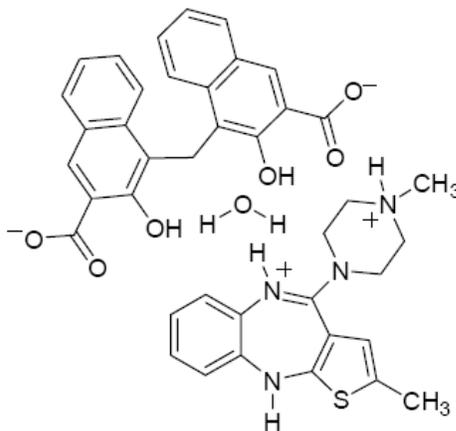
10H-thieno[2,3-b][1,5]benzodiazepine,2-methyl-4-(4-methyl-1-piperazinyl)-,4,4'-methylenebis[3-hydroxy-2-naphthalene-carboxylate](1:1), monohydrate

Chemistry Review Data Sheet

Molecular Formula: $C_{17}H_{22}N_4S \cdot C_{23}H_{14}O_6 \cdot H_2O$

Molecular Weight: 718.8

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
			(b) (4)		4		
					4		

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")

Chemistry Review Data Sheet

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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	8 JAN 2008	S. Ferguson
Pharm/Tox			
Biopharm	Evaluation of dissolution not complete		A. Jackson
EA	Acceptable	22 OCT 2007	Raanan Bloom
Microbiology	Approval	15 FEB 2008	Stephen Langille

Executive Summary Section

The Chemistry Review for NDA 22-173**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

Recommend approval from CMC perspective.

The OCP review team has not completed their evaluation of the dissolution specification. Any changes in the dissolution method or acceptance limits will necessitate a reevaluation of the provided stability data and expiry period.

The CDER Labeling and Nomenclature Committee determined that the most appropriate established name for this product to be “(olanzapine) for extended release injectable suspension” (Attachment 2). This information will need to be relayed to the Applicant.

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

N/A

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)****Drug Substance**

Zyprexa[®] TRADENAME is a sustained release, long-acting parenteral injection (depot) for the chronic or maintenance treatment of psychotic disorders. The active ingredient in the drug product is olanzapine pamoate monohydrate. Olanzapine is the active ingredient in the approved marketed product, Zyprexa[®]. The pamoate salt of the olanzapine molecule provides the drug product with its extended release characteristics.

The chemical name of the drug substance is 10H-thieno[2,3-b][1,5]benzodiazepine,2-methyl-4-(4-methyl-1-piperazinyl)-4,4'-methylenebis[3-hydroxy-2-naphthalene-carboxylate]1:1, monohydrate. Olanzapine pamoate monohydrate is a yellow solid with low solubility in most solvents. Olanzapine pamoate is achiral, but a number of polymorphs have been identified. Olanzapine pamoate can exist in a number of hydrate forms including

Executive Summary Section

the monohydrate crystal form, which was selected for commercial development, and two (b) (4) designated as the (b) (4)

(b) (4),

The applicant manufactures olanzapine pamoate in the monohydrate crystal form. The drug substance will be manufactured at the Eli Lilly S.A., Kinsale, County Cork, Ireland site. (b) (4)

(b) (4)

The applicant has augmented the primary stability data to 24 months on three batches of the DS manufactured at full scale by the commercial process

Executive Summary Section

(b) (4) No changes in physical appearance or crystal form, and no trends in the results for assay, impurities, water, residual solvents, particle size, bacterial endotoxins, total aerobic microbial count, or total combined mold and yeast were detected at the long term storage condition. This satisfactory 24 months stability data supports their re-evaluation period of 36 months, as per ICH Q1E.

Drug Product:

Olanzapine pamoate drug product is a solid, yellow powder in a vial supplied as dosages of 210 mg, 300 mg and 405 mg of olanzapine base (present as the salt, olanzapine pamoate monohydrate 483 mg, 690 mg and 931 mg, respectively). In addition each vial contains an (b) (4) of olanzapine pamoate monohydrate (equivalent to (b) (4) olanzapine base and (b) (4) of final suspension). The package that the health care practitioner receives will consist of a kit with three components: a vial of the drug product (olanzapine pamoate), a vial of viscous aqueous vehicle and a disposable 3 ml syringe with two sterile 1.5 inch 19-gauge needles (Needle Pro cartridges). Immediately prior to administration, the aqueous vehicle is combined with the drug product powder to form a suspension for intramuscular injection (olanzapine pamoate depot). The olanzapine pamoate suspension has a common target concentration of 150 mg/ml olanzapine base for each of the three strengths. The length of drug release (and its bioavailability and the drug product performance) is dependant on the volume introduced and the solid-state properties of the drug substance (each strength has the same concentration). The release is mass (dose) limited and therefore the volume administered decides the length of action.

(b) (4)

Executive Summary Section

The proposed drug product specification will adequately control product quality from a CMC perspective; although at time of completion of this review the OCP review team had not completed their review of the dissolution specification. Batch analyses of one lot of each strength manufactured at full scale at the proposed commercial facility were provided. All results were within the proposed specified limits and were comparable to the clinical lots.

No significant changes were noted in the available primary stability data for the drug product solid after 24 months at 30°C/65%RH. Similarly, minimal changes were observed in the suspension through 24 hours after storage of the solid at 30°C/65%RH up to 12 months; the only significant changes being a decrease in both viscosity and pH; neither of these changes are expected to significantly impact the clinical performance of the administered drug. The stability data support the proposed 36 month expiry period of the drug product powder and the 30°C storage conditions under the current drug product specifications (OCP review team has not completed their review of the dissolution specification).

Olanzapine pamoate vehicle (termed 'diluent' in the product label) is a single-use, sterile, viscous aqueous liquid packaged in a 5 ml Type I glass vial and is used to suspend the olanzapine pamoate drug product.

(b) (4)

Batch analysis data for 12 lots of vehicle were provided. Stability data support a 24 month expiry period for the vehicle. The only significant differences were consistent decreases in pH and viscosity through 24 months and an increase in fine particulate matter between months 12 and 24. These changes are not expected to have a significant impact on the product performance.

(b) (4)

(b) (4) A reduction in the reporting category from Prior Approval Supplement to Annual Report was requested, however it was determined that a reporting category reduction to a CBE-30 would be more appropriate. The Applicant accepted this reporting category in the most recent amendment.

Executive Summary Section

In the previous review cycle, the dosage form designation of ‘long-acting injection’ was referred to members of the Labeling and Nomenclature Committee. They determined that ‘for injectable suspension’ would be a more appropriate term from a CMC perspective as this term is included in the CDER Data Standards Manual. It was thought that the use of the term ‘extended-release’ in the dosage form designation was not appropriate from a CMC perspective as the formulation lacks a specific mechanism to control drug input into the body other than the route (intramuscular) and the low solubility of the suspension formulation. In the course of this review cycle the Labeling and Nomenclature Committee was asked to reconsider their objections and to the use of ‘extended release’ in the established name. They determined that the most appropriate name to be “(olanzapine) for extended release injectable suspension” (Attachment 2).

The review team’s initial hands-on difficulties in attempting the reconstitution with kits provided by the Applicant were discussed at several in-house meetings in the previous review cycle. From the provided CMC data this was not expected to be a problem. However, considering the atypical nature of the multi-step reconstitution procedure, it is conceivable that that some variation may occur depending on the training/thoroughness of the person administering the dose. This reviewer recommends that this issue be addressed through training and product labeling. It was also brought to the attention of the Clinical Division that considering the extensive shaking of the suspension and its slightly viscous nature that all the air bubbles present in the suspension will likely not dissipate prior to administration.

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

The drug product is indicated for treatment of schizophrenia. It is supplied as a kit of three strengths (210 mg, 300 mg and 405 mg). Each kit contains a vial of olanzapine pamoate, a vial of vehicle, a 3 ml syringe and three 19-gauge needles. It is proposed to administer the drug every two weeks in doses of 150 mg, 210 mg or 300 mg or every four weeks in doses of 300 mg or 405 mg. The powder requires reconstitution with the vehicle provided in the kit prior to use. The volume of vehicle added to each strength differs so that they share a common concentration of 150 mg/ml. The reconstitution procedure is not entirely typical for the preparation of an intramuscular suspension, as it involves additional effort to ensure that the powder is completely suspended; this is made more difficult both by the relatively high concentration of solid in the suspension and its yellow color. Although the reconstituted suspension may be stored up to 24 hours at room temperature in the vial, care must be taken to administer the suspension “immediately” after withdrawing it into the syringe. This avoids the settling of the solid in the suspension which may result in blockages of the syringe and injection failures. A 36-month expiry period for

Executive Summary Section

the vials of olanzapine pamoate powder and a 24 month expiry period for the vehicle (both at $\leq 30^{\circ}\text{C}$) was found acceptable from a CMC perspective based on the current specifications (OCP review team has not completed their review of the dissolution specification). The expiry period for the drug product kit will be assigned based on the component (powder or vehicle) with the shortest remaining shelf life.

C. Basis for Approvability or Not-Approval Recommendation

An approval recommendation is being made from CMC perspective based on the data provided and the Applicant's responses to the information requests and deficiencies in the 25 FEB 2008 Not Approvable Letter. An overall acceptable recommendation from the Office of Compliance has been received and an approval recommendation was received from the microbiological review team (15 FEB 2008).

The OCP review team has not completed their evaluation of the dissolution specification. Any changes in the dissolution method or acceptance limits will necessitate a reevaluation of the provided stability data and expiry period.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

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

/s/

David Claffey
10/28/2008 01:38:36 PM
CHEMIST

Ramesh Sood
10/28/2008 02:32:32 PM
CHEMIST

NDA 22-173

**Zyprexa[®] TRADENAME
(Olanzapine) for injectable suspension
210, 300, 405 mg/vial**

**Review#2
Sponsor's Response to IR letter**

Eli Lilly and Company

**Prafull Shiromani Ph. D.
And
David J. Claffey Ph.D**

**Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	Error! Bookmark not defined.
C. Basis for Approvability or Not-Approval Recommendation ...	Error! Bookmark not defined.

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-173
2. REVIEW #: 2
3. REVIEW DATE: 16-Feb-2008
4. REVIEWER: Prafull Shiromani

5. PREVIOUS DOCUMENTS:

Previous Documents

NDA 22-173

Document Date

30-Apr-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA 22-173 Response (CMC)

Document Date

30-Jan-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Eli Lilly and Company
Address: Lilly Corporate Center, Indianapolis, IN 46285
Representative: Robin Pitts Wojcieszek, R.Ph., Associate Director,
U.S. Regulatory Affairs
Telephone: (317) 651-9827

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zyprexa[®] TRADENAME
- b) Non-Proprietary Name (USAN): Olanzapine For Injectable Suspension

Chemistry Review Data Sheet

- c) Code Name/# (ONDC only): LY170053
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 2
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of Schizophrenia

11. DOSAGE FORM: For Injectable Suspension

12. STRENGTH/POTENCY: 210, 300, 405 mg/vial

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

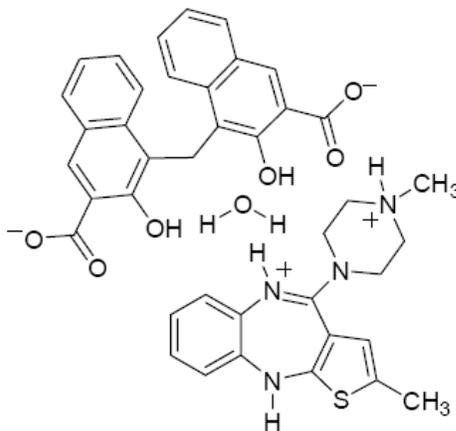
10H-thieno[2,3-b][1,5]benzodiazepine,2-methyl-4-(4-methyl-1-piperazinyl)-,4,4'-methylenebis[3-hydroxy-2-naphthalene-carboxylate](1:1), monohydrate

Chemistry Review Data Sheet

Molecular Formula: $C_{17}H_{22}N_4S \cdot C_{23}H_{14}O_6 \cdot H_2O$

Molecular Weight: 718.8

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					4		
					4		

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")

Chemistry Review Data Sheet

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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	8 JAN 2008	S. Ferguson
Pharm/Tox			
Biopharm	AE. Evaluation of dissolution not complete	12 FEB 2008	A. Jackson
EA	Acceptable	22 OCT 2007	Raanan Bloom
Microbiology	Approval	15 FEB 2008	Stephen Langille

Executive Summary Section

The Chemistry Review for NDA 22-173**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

The application is recommended as “Approvable” from CMC perspective. The following outstanding issues will need to be addressed by the Applicant to the satisfaction of the CMC review team:

(b) (4)

Executive Summary Section

(b) (4)

2. The results of all relevant injectability tests to-date were (b) (4) through the product shelf life. This limit will need to be lowered or evidence provided that the product performance of each of the proposed drug product strengths will not be compromised should their administration require an injection force of (b) (4).

3. Include a requirement that the vehicle's physical appearance be "essentially free from visible particles" (USP <1>) in its release and stability specifications. The in-process visual inspection which you previously referred to does not control this parameter through the proposed shelf-life.

4. The comparability protocol supports a CBE-30 filing. It should be noted that some of the batches used to support this protocol do not meet the acceptance criteria for particle size distribution.

NOTE: The OCP review team has not completed their evaluation of the dissolution specification. Any changes in the dissolution method or acceptance limits will necessitate a reevaluation of the provided stability data and expiration date.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

Zyprexa[®] TRADENAME is a sustained release, long-acting parenteral injection (depot) for the chronic or maintenance treatment of psychotic disorders. The active ingredient in the drug product is olanzapine pamoate monohydrate. Olanzapine is the active ingredient in the approved marketed product, Zyprexa[®].

Executive Summary Section

The pamoate salt of the olanzapine molecule provides the drug product with its extended release characteristics.

The chemical name of the drug substance is 10H-thieno[2,3-b][1,5]benzodiazepine,2-methyl-4-(4-methyl-1-piperazinyl)-4,4'-methylenebis[3-hydroxy-2-naphthalene-carboxylate]1:1, monohydrate. Olanzapine pamoate monohydrate is a yellow solid with low solubility in most solvents. Olanzapine pamoate is achiral, but a number of polymorphs have been identified. Olanzapine pamoate can exist in a number of (b) (4) forms including the monohydrate crystal form, which was selected for commercial development, and two (b) (4) designated as the (b) (4) (b) (4)

The applicant manufactures olanzapine pamoate in the monohydrate crystal form. The drug substance will be manufactured at the Eli Lilly S.A., Kinsale, County Cork, Ireland site. (b) (4)

(b) (4)

Executive Summary Section

(b) (4)

The applicant has augmented the primary stability data to 24 months on three batches of the DS manufactured at full scale by the commercial process (b) (4). No changes in physical appearance or crystal form, and no trends in the results for assay, impurities, water, residual solvents, particle size, bacterial endotoxins, total aerobic microbial count, or total combined mold and yeast were detected at the long term storage condition. This satisfactory 24 months stability data supports their re-evaluation period of 36 months, as per ICH Q1E.

Drug Product:

Olanzapine pamoate drug product is a solid, yellow powder in a vial supplied as dosages of 210 mg, 300 mg and 405 mg of olanzapine base (present as the salt, olanzapine pamoate monohydrate 483 mg, 690 mg and 931 mg, respectively). In addition each vial contains an (b) (4) of olanzapine pamoate monohydrate (equivalent to (b) (4) olanzapine base and (b) (4) of final suspension). The package that the health care practitioner receives will consist of a kit with three components: a vial of the drug product (olanzapine pamoate), a vial of viscous aqueous vehicle and a disposable 3 ml syringe with two sterile 1.5 inch 19-gauge needles (Needle Pro cartridges). Immediately prior to administration, the aqueous vehicle is combined with the drug product powder to form a suspension for intramuscular injection (olanzapine pamoate depot). The olanzapine pamoate suspension has a common target concentration of 150 mg/ml olanzapine base for each of the three strengths. The length of drug release (and its bioavailability and the drug product performance) is dependant on the volume introduced and the solid-state properties of the drug substance (each strength has the same concentration). The release is mass (dose) limited and therefore volume administered decides the length of action

(b) (4)

Executive Summary Section

(b) (4)

The proposed drug product specification will adequately control product quality from a CMC perspective; although at time of completion of this review the OCP review team had not completed their review of the dissolution specification. Batch analyses of one lot of each strength manufactured at full scale at the proposed commercial facility were provided. All results were within the proposed specified limits and were comparable to the clinical lots.

No significant changes were noted in the available primary stability data for the drug product solid after 24 months at 30°C/65%RH. Similarly, minimal changes were observed in the suspension through 24 hours after storage of the solid at 30°C/65%RH up to 12 months; the only significant changes being a decrease in both viscosity and pH; neither of these changes are expected to significantly impact the clinical performance of the administered drug. The stability data support the proposed 36 month expiry period of the drug product powder and the 30°C storage conditions under the current drug product specifications (OCP review team has not completed their review of the dissolution specification).

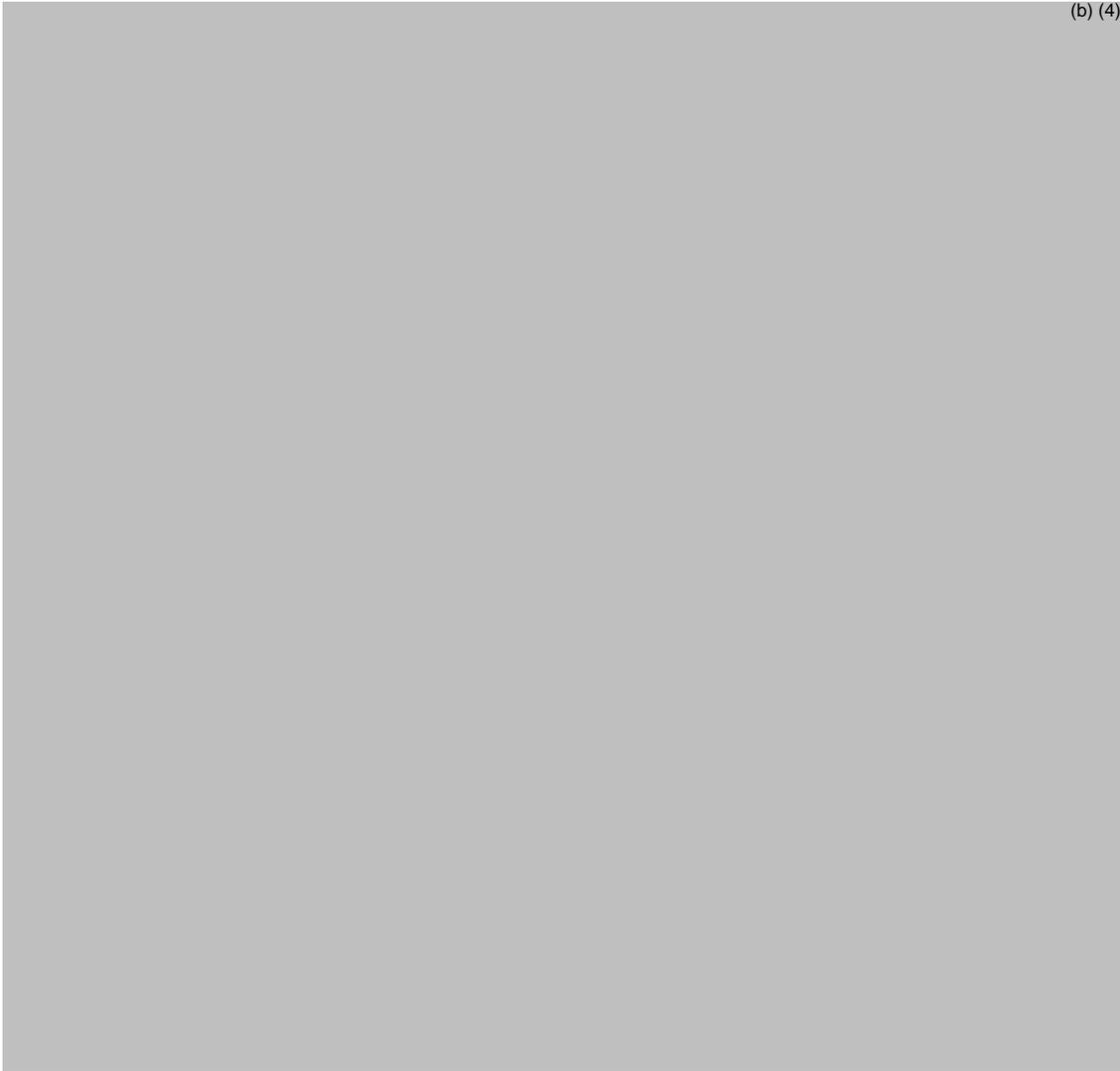
Olanzapine pamoate vehicle (termed 'diluent' in the product label) is a single-use, sterile, viscous aqueous liquid packaged in a 5 ml Type I glass vial and is used to suspend the olanzapine pamoate drug product.

(b) (4)

(b) (4)

Executive Summary Section

(b) (4)



The dosage designation of 'long-acting injection' was referred to members of the Labeling and Nomenclature Committee. They determined that 'for injectable suspension' would be a more appropriate term from a CMC perspective as this term is included in the CDER Data Standards Manual. It was thought that the use of the term 'extended-release' in the dosage form designation was not appropriate from a CMC perspective as the formulation lacks a specific mechanism to control drug input into the body other than the route (intramuscular) and the low solubility of the suspension formulation. This recommendation was relayed to DMETS (Todd Bridges, email 3 JAN 2008). It is expected that DMETS together with the Clinical Division will make the final recommendation.

The review team's initial hands-on difficulties in attempting the reconstitution with kits provided by the Applicant were discussed at several in-house meetings. From the provided CMC data this was not expected to be a problem.

Executive Summary Section

However, considering the atypical nature of the multi-step reconstitution procedure, it is conceivable that that some variation may occur depending on the training/thoroughness of the person administering the dose. This reviewer recommends that this issue be addressed through training and product labeling. It was also brought to the attention of the Clinical Division that considering the extensive shaking of the suspension and its slightly viscous nature that all the air bubbles present in the suspension will likely not dissipate prior to administration.

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

The drug product is indicated for treatment of schizophrenia. It is supplied as a kit of three strengths (210 mg, 300 mg and 405 mg). Each kit contains a vial of olanzapine pamoate, a vial of vehicle, a 3 ml syringe and three 19-gauge needles. It is proposed to administer the drug every two weeks in doses of 150 mg, 210 mg or 300 mg or every four weeks in doses of 300 mg or 405 mg. The powder requires reconstitution with the vehicle provided in the kit prior to use. The volume of vehicle added to each strength differs so that they share a common concentration of 150 mg/ml. The reconstitution procedure is not entirely typical for the preparation of an intramuscular suspension, as it involves additional effort to ensure that the powder is completely suspended; this is made more difficult both by the relatively high concentration of solid in the suspension and its yellow color. Although the reconstituted suspension may be stored up to 24 hours at room temperature in the vial, care must be taken to administer the suspension “immediately” after withdrawing it into the syringe. This avoids the settling of the solid in the suspension which may result in blockages of the syringe and injection failures. A 36-month expiry period for the vials of olanzapine pamoate powder and a 24 month expiry period for the vehicle (both at $\leq 30^{\circ}\text{C}$) was found acceptable from a CMC perspective based on the current specifications (OCP review team has not completed their review of the dissolution specification). The expiry period for the drug product kit will be assigned based on the component (powder or vehicle) with the shortest remaining shelf life.

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended as “Approvable” from CMC perspective. The outstanding deficiencies described above will need to be resolved by the Applicant. An overall acceptable recommendation from the Office of Compliance has been received and an approval recommendation was received from the microbiological review team (15 FEB 2008).

The OCP review team has not completed their evaluation of the dissolution specification. Any changes in the dissolution method or acceptance limits will necessitate a reevaluation of the provided stability data and expiration date.

Executive Summary Section

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

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

/s/

David Claffey
2/19/2008 11:11:16 AM
CHEMIST

Prafull Shiromani
2/19/2008 11:29:52 AM
CHEMIST

Ramesh Sood
2/19/2008 12:16:28 PM
CHEMIST



NDA 22-173

Zyprexa[®] Adhera[™]
Olanzapine “long acting injection”
210, 300, 405 mg/vial

Eli Lilly and Company

Prafull Shiromani, Ph.D.

and

David J. Claffey, Ph.D.

Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation	11
III. Administrative.....	11
A. Reviewer’s Signature	11
B. Endorsement Block	11
C. CC Block.....	12
Chemistry Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	13
S DRUG SUBSTANCE [Name, Manufacturer].....	13
P DRUG PRODUCT [Name, Dosage form].....	101
A APPENDICES	180
R REGIONAL INFORMATION	180
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	182
A. Labeling & Package Insert.....	182
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	192
III. List Of Deficiencies To Be Communicated.....	192

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-173
2. REVIEW #: 1
3. REVIEW DATE: 25 JAN 2008
4. REVIEWER: Prafull Shiromani (Drug Substance) David J. Claffey (Drug Product)

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
NDA 22-173Document Date
30-Apr-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Eli Lilly and Company
Address: Lilly Corporate Center, Indianapolis, IN 46285
Representative: Robin Pitts Wojcieszek, R.Ph., Associate Director,
U.S. Regulatory Affairs
Telephone: (317) 651-9827

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zyprexa[®] Adhera[™]
- b) Non-Proprietary Name (USAN): Olanzapine Long Acting Injection

Chemistry Review Data Sheet

- c) Code Name/# (ONDC only): LY170053
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 2
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of Schizophrenia

11. DOSAGE FORM: For Injectable Suspension

12. STRENGTH/POTENCY: 210, 300, 405 mg/vial

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

Chemical Names (USAN):

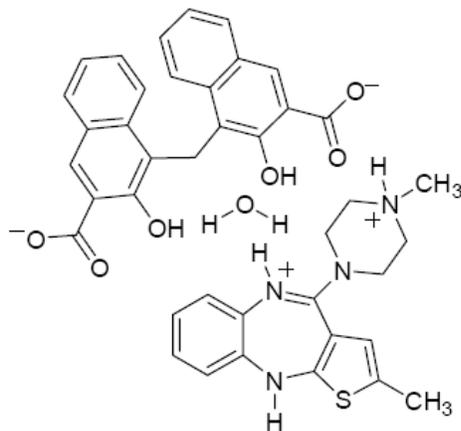
- 1) 2-naphthalenecarboxylic acid, 4-4'-methylenebis[3-hydroxy-, compound with 2-methyl-4-(4-methyl-1-piperazinyl)]-10H-thieno[2,3-b][1,5]benzodiazepine (1:1) monohydrate
- 2) 10H-thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-, 4,4'-methylenebis[3-hydroxy-2-naphthalene-carboxylate] (1:1), monohydrate

Chemistry Review Data Sheet

Molecular Formula: $C_{17}H_{22}N_4S \cdot C_{23}H_{14}O_6 \cdot H_2O$

Molecular Weight: 718.8

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
			(b) (4)		4		
					4		

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")

Chemistry Review Data Sheet

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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	8 JAN 2008	S. Ferguson
Pharm/Tox			
Biopharm	Review not complete		
EA	Acceptable	22 OCT 2007	Raanan Bloom
Microbiology	Review not complete		

Executive Summary Section

The Chemistry Review for NDA 22-173**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

This NDA is recommended as “Approvable” from a CMC perspective. The approvability of this application, from a CMC perspective, depends on the Applicant’s responses to the IR letters dated 21-NOV-2007 and 4 JAN 2008.

The Office of Clinical Pharmacology has not evaluated the proposed dissolution specification at time of completion of this review, therefore a complete evaluation of the drug product specification or of the stability data can not be made at this time.

Approvability will also depend on the recommendation of the microbiology review team; their final recommendation is pending.

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

N/A

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)****Drug Substance**

Zyprexa[®] Adhera[™] is a sustained release, long-acting parenteral injection (depot) for the chronic or maintenance treatment of psychotic disorders. The active ingredient in the drug product is olanzapine pamoate monohydrate. Olanzapine is the active ingredient in the approved marketed product, Zyprexa[®]. The pamoate salt of the olanzapine molecule provides the drug product with its extended release characteristics.

The chemical name of the drug substance is 10H-thieno[2,3-b][1,5]benzodiazepine,2-methyl-4-(4-methyl-1-piperazinyl)-4,4'-methylenebis[3-hydroxy-2-naphthalene-carboxylate]1:1, monohydrate. Olanzapine pamoate monohydrate is a yellow solid with low solubility in most solvents. Olanzapine pamoate is achiral, but a number of polymorphs have been identified. Olanzapine pamoate can exist in a number of hydrate forms including the monohydrate crystal form, which was selected for commercial

Executive Summary Section

development, and two (b) (4) designated as the (b) (4)
(b) (4)

The applicant manufactures olanzapine pamoate in the monohydrate crystal form. The drug substance will be manufactured at the Eli Lilly S.A., Kinsale, County Cork, Ireland site. (b) (4)

(b) (4)

The applicant has provided primary stability data on three batches of the DS manufactured at full scale by the commercial process (b) (4)
(b) (4) Supporting stability data obtained with one drug substance batch manufactured by the development process (b) (4) are also provided. Samples of these four batches were packaged in a small-scale simulator of the commercial container closure system and stored at 25°C/60% RH and 40°C/75% RH. The applicant has obtained eighteen and twenty-four months of long-term term data in the primary and supporting stability studies, respectively. Six months of accelerated data has been obtained in both stability studies. No changes in physical appearance or crystal form, and no trends in the results for assay, impurities, water, residual solvents, particle size, bacterial endotoxins, total aerobic microbial count, or total combined mold and yeast were detected at either storage condition. The provided 18-month long-term stability data support a maximum of 30-month re-test for the drug substance as per ICH Q1E.

Executive Summary Section

Olanzapine pamoate drug product is a solid, yellow powder in a vial supplied as dosages of 210 mg, 300 mg and 405 mg of olanzapine base (present as the salt, olanzapine pamoate monohydrate 483 mg, 690 mg and 931 mg, respectively). In addition each vial contains an (b) (4) olanzapine pamoate monohydrate (equivalent to (b) (4) olanzapine base and (b) (4) of final suspension). The package that the health care practitioner receives will consist of a kit with three components: a vial of the drug product (olanzapine pamoate), a vial of viscous aqueous vehicle and a disposable 3 ml syringe with two sterile 1.5 inch 19-gauge needles (Needle Pro cartridges). Immediately prior to administration, the aqueous vehicle is combined with the drug product powder to form a suspension for intramuscular injection (olanzapine pamoate depot). The olanzapine pamoate suspension has a common target concentration of 150 mg/ml olanzapine base for each of the three strengths.

(b) (4)

(b) (4)

The proposed drug product specification will adequately control product quality from a CMC perspective; although at time of completion of this review the OCP review team had not completed their review of the dissolution specification. Batch analyses of one lot of each strength manufactured at full scale at the proposed commercial facility were provided. All results were within the proposed specified limits and were comparable to the clinical lots.

No significant changes were noted in the available primary stability data for the drug product solid after 12 months at 30°C/65%RH. Similarly, minimal changes were observed in the suspension through 24 hours after storage of the solid at 30°C/65%RH up to 12 months; the only significant changes being a decrease in both viscosity and pH; neither of these changes are expected to significantly impact the clinical performance of the administered drug. Additionally, the levels of unspecified

Executive Summary Section

impurities approached the proposed (b) (4) limit in some batches, therefore the Applicant was asked to provide additional stability data to support the proposed (b) (4) expiry period and the 30°C storage conditions.

Olanzapine pamoate vehicle is a single-use, sterile, viscous aqueous liquid packaged in a 5 ml Type I glass vial and is used to suspend the olanzapine pamoate drug product.

(b) (4)

(b) (4)

The dosage designation of 'long-acting injection' was referred to members of the Labeling and Nomenclature Committee. They determined that 'for injectable suspension' would be a more appropriate term from a CMC perspective as this term is included in the CDER Data Standards Manual. It was thought that the use of the term 'extended-release' in the dosage form designation was not appropriate from a CMC perspective as the formulation lacks a specific mechanism to control drug input into the body other than the route (intramuscular) and the low solubility of the suspension formulation. This recommendation was relayed to DMETS (Todd Bridges, email 3 JAN 2008). It is expected that DMETS together with the Clinical Division will make the final recommendation.

This reviewer received a sample of the drug product kit (4 JAN 2008) and met with the clinical review team and DMETS review team (4 JAN 2008) so that its reconstitution could be evaluated first-hand. The medical reviewer attempted to follow the reconstitution instructions for the 300 mg strength product. After reconstitution, just 1.7 ml (ca. 85%) of the required 2.0 ml of suspended material could be drawn into the syringe, although there did appear to be some suspension remaining adhered to the sides of the vial. The Clinical Division was made aware of this occurrence. They were

Executive Summary Section

advised that CMC data such as the results of the injection efficiency experiments and the (b) (4) indicate that this was not an issue. However, considering the atypical nature of the multi-step reconstitution procedure, it is conceivable that that some variation may occur depending on the training/thoroughness of the person administering the dose. It was also brought to the attention of the Clinical Division that considering the extensive shaking of the suspension and its slightly viscous nature that all the air bubbles present in the suspension will likely not be removed prior to administration.

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

The drug product is indicated for treatment of schizophrenia. It is supplied as a kit of three strengths (210 mg, 300 mg and 405 mg). Each kit contains a vial of olanzapine pamoate, a vial of vehicle, a 3 ml syringe and three 19-gauge needles. It is proposed to administer the drug every two weeks in doses of 150 mg, 210 mg or 300 mg or every four weeks in doses of 300 mg or 405 mg. The powder requires reconstitution with the vehicle provided in the kit prior to use. The volume of vehicle added to each strength differs so that they share a common concentration of 150 mg/ml. The reconstitution procedure is not entirely typical for the preparation of an intramuscular suspension, as it involves additional effort to ensure that the powder is completely suspended; this is made more difficult both by the relatively high concentration of solid in the suspension and its yellow color. Care must be taken to administer the suspension “immediately” after withdrawing it into the syringe. This avoids the settling of the solid in the suspension which may result in blockages of the syringe and injection failures. A (b) (4) (b) (4) expiry period for the kit at $\leq 30^{\circ}\text{C}$ has been proposed. The reconstituted suspension may be stored up to 24 hours at room temperature.

C. Basis for Approvability or Not-Approval Recommendation

Approvability will depend on the sponsor’s response to FDA review comments submitted through an IR-letters dated 21-NOV-2007 and 4 JAN 2008 and an approval recommendation from the OCP and microbiological reviewers. An overall acceptable recommendation has been received from the Office of Compliance.

III. Administrative**A. Reviewer’s Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

Executive Summary Section

C. CC Block

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

/s/

David Claffey
1/30/2008 11:50:52 AM
CHEMIST

Prafull Shiromani
1/31/2008 11:55:50 AM
CHEMIST

Ramesh Sood
1/31/2008 12:32:45 PM
CHEMIST

Initial Quality Assessment Branch I

OND Division: Division of Psychiatry Products
NDA: 22-173
Applicant: Eli Lilly and Company
Letter Date: 27-APR-07
Stamp Date: 30-APR-07
PDUFA Date: 29-FEB-08
Trademark: Zyprexa® Ahdera™
Established Name: olanzapine pamoate
Dosage Form: Injection
Route of Administration: Intramuscular Injection
Indication: Schizophrenia
Assessed by: Thomas F. Oliver, Ph.D.

Summary and Critical Issues:

Summary

Zyprexa® Ahdera™ (olanzapine pamoate) was developed for the treatment of schizophrenia. Eli Lilly has investigated the use of olanzapine pamoate in various psychiatric disorders (IND 60,701, AT 09-AUG-00). The applicant has three approved olanzapine products: 1) Zyprexa Tablets [NDA 20-592, AP, 30-SEP-96], 2) Zyprexa Zydis Orally Disintegrating Tablets [NDA 21-086, AP, 06-APR-00], and 3) Zyprexa IM [NDA 21-253, AP, 29-MAR-04]. The applicant had a CMC meeting (22-JUL-03) to discuss a number of issues including starting materials, and drug substance and drug product stability protocols and a meeting (09-SEP-05) to discuss comparability of the two (b) (4) and the dissolution method. In addition, the applicant had a meeting (22-FEB-06) with the ONDQA IO and OPS to discuss the (b) (4) (b) (4) to measure tablet weights. Minutes for these meetings can be found in DFS and should be read by the assigned reviewer(s).

Drug Substance

Olanzapine pamoate monohydrate is a yellow solid with low solubility in most solvents. Olanzapine pamoate is achiral, but a number of polymorphs have been identified. Olanzapine pamoate can exist in a number of hydrated forms including the monohydrate crystal form which was selected for commercial development and two different (b) (4) (b) (4) designated as the (b) (4) and the (b) (4). The sponsor also identified several solvated forms of olanzapine pamoate: (b) (4)

The applicant manufactures olanzapine pamoate in the monohydrate (b) (4). The drug substance will be manufactured at the Eli Lilly S.A., Kinsale, County Cork,

Ireland site.

(b) (4)

Drug Product

Olanzapine pamoate depot consists of two components: a single-use vial of the drug product [210-, 300-, and 405-mg of olanzapine base (present as the salt, olanzapine pamoate monohydrate)]; and a single-use vial of sterile aqueous vehicle (b) (4). Immediately prior to administration, the aqueous vehicle is combined with the drug product powder to form a suspension for intramuscular injection (olanzapine pamoate depot). The olanzapine pamoate suspension has a target concentration of 150 mg/mL olanzapine base for all dosage strengths. The injection is to be given every 2 to 4 weeks as a deep intramuscular gluteal injection.

(b) (4) of olanzapine pamoate monohydrate drug substance into vials (b) (4)

The drug product will be manufactured at Eli Lilly (Indianapolis, IN). The drug product will be (b) (4)

The vehicle is composed Carboxymethylcellulose sodium, Mannitol, polysorbate 80, water for injection, and sodium hydroxide/hydrochloric acid (pH adjustment) and will be manufactured by (b) (4) Olanzapine pamoate vehicle is (b) (4)

The microbial control of olanzapine pamoate vehicle is assured by sterility and endotoxin specifications. In addition, the excipients are tested for microorganisms and endotoxins. (b) (4)

(b) (4) and the container closure system has been demonstrated to be integral to vehicle sterility using the microbial ingress methods. The sterile aqueous vehicle is supplied in a (b) (4) glass vial, closed with a (b) (4) (b) (4). The applicant has requested a (b) (4) for the vehicle stored in vials at room temperature. The sponsor states that the drug product when suspended in the vehicle is stable at room temperature for 8 hours.

Critical Issues for Review

• The sponsor has identified a number of possible hydrates and solvates of the olanzapine pamoate. It will need to be determined whether the sponsor understands the factors/conditions that are involved in the formation of the various polymorphs (b) (4) and has appropriate controls in place to produce pure monohydrate. In addition, the (b) (4) used for drug substance release testing will need to have adequate selectivity to distinguish the monohydrate from small amounts of the (b) (4) and the (b) (4)

• The effect of manufacturing operations (b) (4)
(b) (4)

(b) (4) and (b) (4) are designated as starting materials for the commercial manufacture of olanzapine pamoate monohydrate. The starting material, (b) (4) manufactured by Eli Lilly S.A. – Irish Branch, Kinsale, Ireland, is approved in the United States in NDA 21-253 as the drug substance for the rapid acting intramuscular pharmaceutical form of Zyprexa. The acceptability of the starting materials and the corresponding acceptance specifications will need to be determined (refer to CMC meeting minutes).

• The applicant has used a number of manufacturing processes (b) (4) (b) (4) during the development of the olanzapine pamoate monohydrate before settling on the commercial (b) (4). The commercial (b) (4) was used to generate batches that were used in the primary stability studies, LOBS(a), HGKB, HGLQ and clinical trial. However, it will need to be determined whether the drug substance manufactured using this pathway is different (chemically or physically) from what was used earlier (e.g., toxicology) and if any of these differences could have clinical implications.

• As olanzapine is known to degrade in the presence of water [primarily Compound (b) (4) and Compound (b) (4) the (b) (4) is very important in controlling the level of impurities (b) (4). The sponsor has performed a number of DOE studies evaluating five parameters (b) (4). In addition, it will need to be determined what changes in the manufacturing process (e.g., type or size of vessel, process scale, reaction conditions) could result in possible problems and how these changes should be covered post-approval.

• The adequacy of the (b) (4) specifications will need to be determined.

• The applicant (b) (4) the drug substance and has set both a drug substance particle size specification (b) (4) and a specific surface area specification. The sponsor will need to demonstrate that particle size/surface area as measured in clinical, stability, and

commercial batches is rationally controlled (i.e., specification limits) to ensure commercial product performance (as outlined in labeling).

[Redacted] (b) (4)

- The acceptability of impurity specification limits for Compounds [Redacted] (b) (4) and [Redacted] (b) (4) will need to be determined in conjunction with pharm/tox and in context with what has been approved.

- The sponsor states that during the manufacture of the drug substance, material that does not conform to specification or other standards may be reprocessed by repeating part of or all of the established manufacturing process. This issue will need to be evaluated and it will need to be determined if adequate controls are in place.

- The stability of the drug substance will need to be evaluated and the adequateness of the simulated stability container will need to be determined. The effect of stressing conditions, including light, on the stability of the drug substance will need to be determined.

- [Redacted] (b) (4)
Subsequent development resulted in a validated [Redacted] (b) (4) [Redacted] (b) (4) that was used for the Phase 3 clinical trial batches. The applicant controls [Redacted] (b) (4) [Redacted] (b) (4) as described in Section 3.2.P.3.3.2, Description of the Manufacturing Process. The microbiology sections of the drug substance, drug product, and vehicle will need to be consulted to the Microbiology group.

[Redacted] (b) (4)

- The sponsor has an (b) (4) of olanzapine (or (b) (4) olanzapine pamoate monohydrate) in each vial (for each dosage strength). It will need to be determined whether the sponsor has demonstrated that this overage is acceptable for delivering the label claim.
- The effect of (b) (4) on particle size, (b) (4) structure and impurities should be evaluated. The sponsor does not have a specification for particle size or (b) (4) structure as part of the drug product specification.
- The compatibility of the excipients used in the vehicle will need to be evaluated.
- The acceptability of the specifications for the drug product vehicle will need to be evaluated, including the microbial specification limits and the pH specification limit of (b) (4). The effect of the pH on drug release will need to be determined in context of setting appropriate pH limits.
- The adequacy of the vehicle container closure system (Type I glass vial, rubber stopper, sealed with aluminum seal, (b) (4)) will need to be determined.
- The compatibility of the vehicle and of the olanzapine pamoate drug product with the container closure should be evaluated (e.g., adequacy of compatibility and leachable studies).
- The label lists olanzapine and it is expressed as the free base olanzapine [e.g., the 210 mg strength is listed as 210 mg olanzapine. It contains 483 mg of olanzapine pamoate].

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. As the NDA is extensive and contains elements of QbD (including DOE studies and inclusion of a (b) (4) (b) (4)

(b) (4) a team review should be employed. As Dr. Sherita McLamore has been involved in some of the CMC meetings with this product and has worked on other Zyprexa products, she should one member of the team.

The applicant has claimed a categorical exclusion to the environmental assessment [below 1 part per billion at the point of entry into the aquatic environment; 21 CFR 25.31 (b)] and stated that there are no extraordinary circumstances for this proposed action (introduction of olanzapine). The applicant has argued that since the formation of a salt (pamoate) and changing the route of administration will not alter the pharmacology or the human metabolite excretion profile of olanzapine, it is appropriate to consider only olanzapine in assessing potential environmental impact. This argument will need to be brought to the attention of the EA staff for verification.

The microbiology sections of the drug substance, drug product, and vehicle will need to be consulted to the Microbiology group.

The sites were submitted into EES (14-JUN-07 by T.Oliver), however, the reviewer(s) will need to confirm that these are the only sites.

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

/s/

Thomas Oliver
6/15/2007 07:48:04 AM
CHEMIST

Ramesh Sood
6/19/2007 12:47:35 PM
CHEMIST