CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213378Orig1s000
213378Orig2s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213378
Assessment 2

Drug Product Name	olanzapine and samidorphan tablets
Dosage Form	tablet
Strength	5 mg olanzapine/10 mg samidorphan 10 mg olanzapine/10 mg samidorphan 15 mg olanzapine/10 mg samidorphan 20 mg olanzapine/10 mg samidorphan
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Alkermes, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document # 21; eCTD 0020	1 Dec 20	Process; facilities

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	N/A	N/A
Manufacturing	Teng (Daisy) Xu	Sharmista Chatterjee
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The CMC recommendation is approval for this application based on the process/facilities review. The original reviews for drug product, drug substance and biopharmaceutics recommended approval and they remain approval in this review cycle.

The proposed shelf-life of 30 months, when stored at controlled room temperature (20°C to 25°C), is acceptable.

See also original IQA dated 15 Jul 20 and process/facilities addendum dated 15 Oct 20.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This product is a film-coated, immediate release, fixed-dose combination bilayer tablets (b) (4) (b) (4) It is indicated for the treatment of schizophrenia and bipolar I disorder.

A complete response letter (CRL) dated 13 Nov 20 was sent to the applicant. This resubmission is the response to that CRL.

See also original IQA dated 15 Jul 20 and process/facilities addendum dated 15 Oct 20.

The proposed shelf-life of 30 months, when stored at controlled room temperature (20°C to 25°C), is acceptable.

Proposed Indication(s) including Intended Patient Population	The treatment of schizophrenia and bipolar I disorder
Duration of Treatment	chronic
Maximum Daily Dose	Olanzapine 20 mg / samidorphan 10 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

See original IQA dated 15 Jul 2020.

Drug Product: Adequate

See original IQA dated 15 Jul 2020.

Labeling: Adequate

Manufacturing: Adequate

(b) (4)

See also process and facilities IQA addendum dated 15 Oct 20.

Biopharmaceutics: Adequate

See original IQA dated 15 Jul 2020.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled by specification	Acceptable	

Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	M	Controlled by specification	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	H	Controlled by specification	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled by specification	Acceptable	
Dissolution – BCS Class III	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled by specification	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	3	21 Apr 20	Yuefeng (Simon) Peng
	II			3	15 Aug 18	Ben Zhang
	II			1	26 May 20	Gaetan Ladouceur
	III			4		
	III			4		
	III			4		

Action codes for DMF Table:
1 – DMF Reviewed.
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")

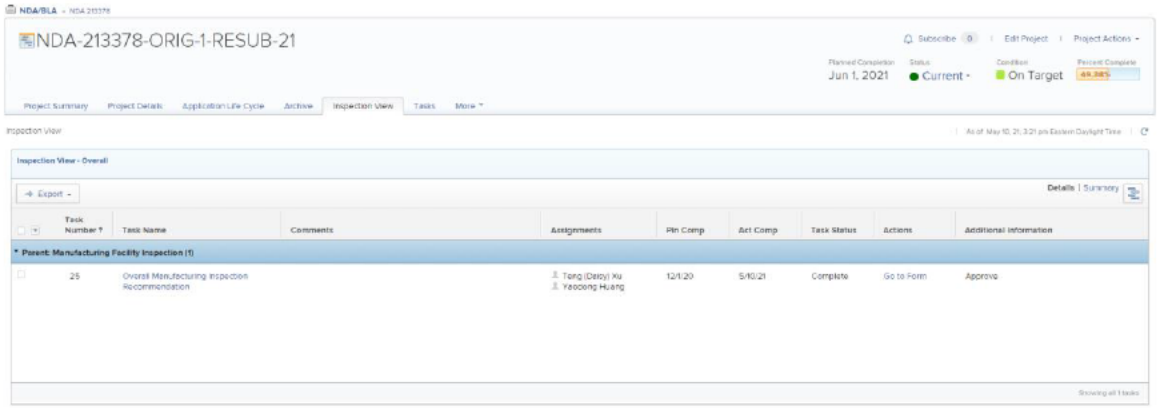
B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	020592	Zyprexa
IND	114375	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Screenshot showing approval recommendation from facilites (taken 10 May 21)



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/s/

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
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NDA 213378
Assessment 1

Drug Product Name	olanzapine and samidorphan tablets
Dosage Form	tablet
Strength	5 mg olanzapine/10 mg samidorphan 10 mg olanzapine/10 mg samidorphan 15 mg olanzapine/10 mg samidorphan 20 mg olanzapine/10 mg samidorphan
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Alkermes, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document # 1; eCTD 0001	15 Nov 2019	Original NDA submission
Supporting document # 8; eCTD 0008	12 Jun 20	Process
Supporting document # 9; eCTD 0009	12 Jun 20	Drug product
Supporting document # 11; eCTD 0011	26 Jun 20	Process
Supporting document # 15; eCTD 0015	11 Sep 20	Process and facilities

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Mariappan Chelliah	Julia Pinto
Manufacturing	Teng (Daisy) Xu	Yaodong (Tony) Huang
Microbiology	N/A	N/A
Biopharmaceutics	Assadollah Noory	Ta-Chen Wu

Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Mariappan Chelliah	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends complete response for this application due to facilities deficiencies. Based on the review of the information submitted drug product, drug substance and biopharmaceutics recommend approval, see the original CMC IQA dated 15 Jul 20. The purpose of this addendum is to include the facilities inspection and process review.

The proposed shelf-life of 30 months, when stored at controlled room temperature (20°C to 25°C), is acceptable.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This product is a film-coated, immediate release, fixed-dose combination bilayer tablets (b) (4) (b) (4) It is indicated for the treatment of schizophrenia and bipolar I disorder.
The proposed shelf-life of 30 months, when stored at controlled room temperature (20°C to 25°C), is acceptable.

Proposed Indication(s) including Intended Patient Population	The treatment of schizophrenia and bipolar I disorder
Duration of Treatment	chronic
Maximum Daily Dose	Olanzapine 20 mg / samidorphan 10 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

See original CMC IQA dated 15 Jul 20

Drug Product: Adequate

See original CMC IQA dated 15 Jul 20

Labeling: Adequate

See original CMC IQA dated 15 Jul 20

Manufacturing: Inadequate

Olanzapine and samidorphan tablets, 5/10, 10/10, 15/10, 20/10 mg/mg strength are film-coated, immediate-release, fixed-dose combination, bilaver tablets. (b) (4) (b) (4)

Alkermes, Inc. /FEI: 1000142940 is proposed as drug product manufacturing facility. (b) (4) (b) (4) PAI is requested for the drug product manufacturing facility. PAI was originally scheduled for April 2020. However, due to the COVID-19 pandemic, 704 (a) (4) was conducted in lieu of on-site inspection.

Withhold recommendation is made based on the observation that the firm failed to establish (b) (4) (b) (4) (b) (4) The detailed assessment can be found in Section II-9 of the process and facilities review.

Biopharmaceutics: Adequate

See original CMC IQA dated 15 Jul 20

Microbiology (if applicable): Choose an item.

N/A

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

Deficiency 1:
During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, and provided by Alkermes, Inc./FEI: 1000142940, Wilmington, OH, USA manufacturing facility, the FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved.

If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-andresponse/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documentsindustry-fda-staff-and-other-stakeholders

Deficiency 2:
(b) (4)

(b) (4)

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

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/s/

VALERIE R AMSPACHER
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Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Alkermes, Inc.
US agent, if applicable	N/A

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Supporting document # 11; eCTD 0011	26 Jun 20	Process

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Mariappan Chelliah	Julia Pinto
Manufacturing	Teng (Daisy) Xu	Yaodong (Tony) Huang
Microbiology	N/A	N/A
Biopharmaceutics	Assadollah Noory	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	

Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Mariappan Chelliah	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

A CMC recommendation is pending facilities inspection and process review. Based on the review of the information submitted drug product, drug substance and biopharmaceutics recommend approval. Once the process and facility review is complete, an addendum with the final, overall CMC approvability recommendation will be added in Panorama and DARRTS.

The proposed shelf-life of 30 months, when stored at controlled room temperature (20°C to 25°C), is acceptable.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This product is a film-coated, immediate release, fixed-dose combination bilayer tablets (b) (4) (b) (4) It is indicated for the treatment of schizophrenia and bipolar I disorder.
The proposed shelf-life of 30 months, when stored at controlled room temperature (20°C to 25°C), is acceptable.

Proposed Indication(s) including Intended Patient Population	The treatment of schizophrenia and bipolar I disorder
Duration of Treatment	chronic
Maximum Daily Dose	Olanzapine 20 mg / samidorphan 10 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

This NDA application (Lybalvi oral tablets) is a combination of two drug substances: samidorphan and olanzapine.

Samidorphan is a new molecular entity. It is not hygroscopic (b) (4) (b) (4)

Specified and unspecified impurities are controlled to qualified level or to the ICH Q3A identification thresholds, respectively. (b) (4) is the sole specified impurity listed in the drug substance specification (b) (4) (b) (4)

As per the analysis of the Pharm/Tox reviewer (Dr. Amy Avila), a limit of (b) (4)% listed in the drug substance specification provides a (b) (4) safety margin for a dose of 10 mg samidorphan compared to the animal NOAEL. Only one impurity (b) (4) was identified as potentially genotoxic in accordance with the classification scheme outlined in ICH M7. It is controlled at (b) (4) ppm in the specification (b) (4) (b) (4) as per the highest daily dose of samidorphan (10 mg) to be administered.

The drug substance retest period is (b) (4) months while stored at no more than (b) (4) °C in the proposed container closure system.

Olanzapine USP is an antipsychotic drug approved by the FDA since 1996. The drug substance information is cross-referenced to DMF (b) (4) which was last reviewed by the Agency on 05/25/2020 (adequate).

Drug Product: Adequate

ALKS 3831 oral tablets are film-coated, immediate release, fixed-dose combination bilayer tablets (b) (4) (b) (4) All the excipients (b) (4) (b) (4) are of compendial grade and their qualities are controlled by their respective compendial testing methods. The Applicant has adequately validated all the non-compendial analytical methods and they are suitable for controlling the quality of the drug product. The drug product will be packaged in the following commercial presentations: 7-ct, 30-ct, 90-ct in HDPE bottles with desiccant and fitted with a (b) (4) child-resistant (CR) closure.

The Applicant has provided up to 18 months of long-term and 6 months of accelerated stability data for the primary batches. In addition, up to 6 months of long-term and accelerated stability data are also available for the supportive batches. No trending is noted for any of the tested attributes. (b) (4) (b) (4) The proposed shelf-life of 30 months, when stored at controlled room temperature (20°C to 25°C), is acceptable.

Although samidorphan is a new molecular entity, a Method Verification Request was not submitted to the Office of Testing and Research, Division of Pharmaceutical Analysis (DPA) in St. Louis. The drug product reviewer determined that the applicant's proposed analytical procedures for quality control and regulatory purposes were adequate and no verification was needed.

Labeling: Adequate

Manufacturing: Choose an item.

Process and facility assessment is currently pending. No recommendation is made from process or facilities at this time. Once the process and facility review is complete, an addendum with the final approvability recommendation will be added in Panorama and DARRTS.

Biopharmaceutics: Adequate

The Biopharmaceutics review was focused on evaluation of (1) the adequacy of the proposed dissolution method and acceptance criterion, (2) formulation bridging throughout product development between the to-be-marketed drug product to the formulations used in clinical studies, and (3) risk assessment.

1) Dissolution Method and Acceptance Criterion:
The proposed dissolution method [USP Apparatus 2 ((paddle) with sinker at 75 rpm in 500 ml of 0.1N HCl, /37°C] and acceptance criterion [NLT (b) (4)% (Q) in 30 minutes] for the proposed drug product at batch release and on stability testing are deemed acceptable, based on the totality of the information and data provided (e.g., aqueous solubility, rapid (b) (4) (b) (4) dissolution in 0.1N HCl medium, and the control of API particle size).
The Applicant identified the rate-limiting step (b) (4) (b) (4) The proposed dissolution method was demonstrated to have the discriminating ability toward selected attributes that may have impact on drug release (b) (4) (b) (4)

2) Formulation Bridging Throughout Product Development:
For waiver of in vivo BE study between the ALKS 3831 to-be-marketed formulation (Formulation A) and clinical trial formulations (Formulations B and C) used in pivotal Phase 3 studies comparative dissolution profiles were provided using pH 1 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer bridging formulation A to formulation B and C. All three

formulations showed rapid and similar dissolution profiles in all media tested.
3) Biopharmaceutics Risk Assessment:
The product risk associated with dissolution and bioavailability is considered "low" from a Biopharmaceutics standpoint as both drug substances have high solubility over physiologic pH range 1.0 to 6.8, with control of API particle sizes. Additionally, the Tmax of the active ingredients is not considered critical regarding treatment effect or disease control for the proposed indication.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled by specification	Acceptable	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	M	Controlled by specification	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	H	Controlled by specification	Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled by specification	Acceptable	

Dissolution – BCS Class III	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled by specification	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments

(b) (4)		(b) (4)		
	II		21 Apr 20	Yuefeng (Simon) Peng
	II		15 Aug 18	Ben Zhang
	II		26 May 20	Gaetan Ladouceur
	III			
	III			
	III			

Action codes for DMF Table:
1 – DMF Reviewed.
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")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	020592	Zyprexa
IND	114375	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				

Clinical				
Other				

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	LYBALVI	adequate
Established name(s)	olanzapine and samidorphan	adequate
Route(s) of administration	for oral use	adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets (olanzapine/samidorphan): 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	n/a	n/a

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	adequate
Strength(s) in metric system	5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg	adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Strength for the samidorphan is based on on free base	adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Color, shape, and marking are included	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Description contains both Trade and established names	adequate
Dosage form(s) and route(s) of administration	Tablets; oral administration	adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Samidorphan is a salt of L-malate and its equivalency statement is included.	adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Statement of being sterile (if applicable)	n/a	n/a
Pharmacological/ therapeutic class	Yes	adequate
Chemical name, structural formula, molecular weight	Yes	adequate
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa or pH)	pKa values are includes	adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	n/a
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	n/a

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	adequate
Strength(s) in metric system	5/10, 10/10, 15/10, 20/10	adequate
Available units (e.g., bottles of 100 tablets)	7-count; 30-count; 90-count	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Color, debossing, and NDC#s are included.	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Protect from moisture	adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Yes	adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	20°C to 25°C (68°F to 77°F)	adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	n/a
Include information about child-resistant packaging	child resistant closure	adequate

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Alkermes, Inc. 852 Winter Street Waltham, MA 02451-1420	adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

As a representative example, a copy of the carton label for 5 mg/10 mg strength, 30 tablets packaging configuration from SN0001 is provided below:

3.2 Carton Labeling

As a representative example, a carton of the carton label for 5 mg/10 mg strength, 30 tablets packaging configuration from SN0001 is provided below:


(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	LYBALVI (large font) olanzapine/samidorphan (small font)	We will ask the Applicant to edit the non-proprietary name as follows: "(olanzapine and samidorphan)" Adequate pending edit.
Dosage strength	5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg	adequate
Route of administration	oral	adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Salt equivalency statement for samidorphan is lacking currently. We will send an IR asking to include this statement.	adequate (pending edit)
Net contents (e.g. tablet count)	7 tablets/30 tablets/90 tablets	adequate
"Rx only" displayed on the principal display	Yes	adequate
NDC number	Yes	adequate
Lot number and expiration date	Yes	adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	n/a	n/a
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	n/a
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	n/a	n/a

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Bar code	Yes	adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	adequate
Medication Guide (if applicable)	Yes	adequate
No text on Ferrule and Cap overseal	n/a	n/a
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	n/a	n/a
And others, if space is available	n/a	n/a

Assessment of Carton and Container Labeling: *Adequate*
Except for the salt equivalency statement and the non-proprietary name, the proposed carton and container labels meet appropriate regulatory requirements from a product quality perspective. We will be sending an IR asking the Applicant to include the salt equivalency statement for samidorphan in the carton label and edit the non-proprietary name as "(olanzapine and samidorphan)".

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

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Julia Pinto

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-213378-ORIG-1
Drug Product Name	LYBALVI™ (olanzapine and samidorphan) Tablets
Dosage Form/ Strength	Tablet, 5/10, 10/10, 15/10, 20/10 mg/mg
Route of Administration	Oral
Applicant Name	Alkermes, Inc.
Therapeutic Classification/ OND Division	Antipsychotics/Schizophrenia/DP
Proposed Indication	Treatment of Schizophrenia and Bipolar I Disorder
Submission Date	11/15/2019 (Original)
Primary Reviewer	Assadollah Noory, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.
Assessment Recommendation	**Adequate**

Background:

The Applicant is seeking 505(b)(2) approval for the proposed Lybalvi™ (olanzapine and samidorphan) Tablets, 5/10, 10/10, 15/10, 20/10 mg/mg (olanzapine/samidorphan), immediate-release, fixed-dose combination, film-coated bilayer tablets, for the treatment of Schizophrenia and Bipolar I Disorder. Samidorphan (SAM) is included to mitigate Olanzapine (OLZ)-induced weight gain. The recommended dose is 10/10, 15/10, or 20/10 administered orally, once daily, without regard to food, with starting dose being 5/10 or 10/10 for schizophrenia and 10/10 or 15/10 for Bipolar I Disorder.

Assessment Summary:

The Biopharmaceutics review was focused on evaluation of (1) the adequacy of the proposed dissolution method and acceptance criterion, (2) formulation bridging throughout product development between the to-be-marketed drug product to the formulations used in clinical studies, and (3) risk assessment.

1) Dissolution Method and Acceptance Criterion:

The proposed dissolution method [USP Apparatus 2 ((paddle) with sinker at 75 rpm in 500 ml of 0.1N HCl, /37°C] and acceptance criterion [NLT (b) (4)% (Q) in 30 minutes] for the proposed drug product at batch release and on stability testing are deemed acceptable, based on the totality of the information and data provided (e.g., aqueous solubility, rapid (b) (4) dissolution in 0.1N HCl medium, and the control of API particle size).

The Applicant identified the rate-limiting step (b) (4) (b) (4) The proposed dissolution method was demonstrated to have the discriminating ability toward selected attributes that may have impact on drug release (b) (4) (b) (4)

2) Formulation Bridging Throughout Product Development:

For waiver of in vivo BE study between the ALKS 3831 to-be-marketed formulation (Formulation A) and clinical trial formulations (Formulations B and C) used in pivotal Phase 3 studies comparative dissolution profiles were provided using pH 1 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer bridging formulation A to formulation B and C. All three formulations showed rapid and similar dissolution profiles in all media tested.

3) Biopharmaceutics Risk Assessment:

The product risk associated with dissolution and bioavailability is considered "low" from a Biopharmaceutics standpoint as both drug substances have high solubility over physiologic pH range 1.0 to 6.8, with control of API particle sizes. Additionally, the Tmax of the active ingredients is not considered critical regarding treatment effect or disease control for the proposed indication.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 213378 for the proposed LYBALVI™ (olanzapine and samidorphan) Tablets, 5/10, 10/10, 15/10, 20/10 mg/mg, are adequate and acceptable for APPROVAL.

FDA-approved dissolution method and acceptance criterion for the proposed LYBALVI™ (olanzapine and samidorphan) Tablets of four strengths:

Dissolution method and acceptance criterion for LYBALVI™ (olanzapine and samidorphan) tablets				
USP Apparatus	**Speed**	**Medium**	**Volume/Temp**	**Acceptance Criterion**
2 (Paddle) With sinker	75 rpm	0.1N HCl	500 mL/37°C	NLT (b) (4)% (Q) at 30 minutes

REVIEWER ASSESSMENT:

List Submissions being assessed:

Document(s) Assessed	Date Received
Original Submission	11/15/2019
Response to Quality Information Request	13/03/2020

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

B.1 BCS DESIGNATION

Assessment: *A BCS designation is not requested.*

The Applicant claimed that the proposed tablet drug product belongs to the Biopharmaceutics Classification System (BCS) Class 3 because olanzapine and samidorphan exhibit high solubility (over pH range of 1 to 6.8) and low permeability based on [^{14}C] mass balance studies.

Solubility:

Olanzapine and samidorphan have high solubility over a pH range of 1 to 6.8. Solubility measurements of olanzapine and samidorphan were determined over pH range (b) (4) Three pH tests conditions (i.e., pH (b) (4)) were selected to determine the solubility profile of both olanzapine and samidorphan L-malate drug substances. For the highest strength/dose, (b) (4) (b) (4) is required to dissolve 20 mg olanzapine and 10 mg samidorphan. Given that, sink conditions for dissolution testing was achieved. SAM L-malate solubility was also determined in simulated fluids at (b) (4) and 37 °C based on Agency Preliminary Comments (Type C Meeting, April 2018) (Table 1).

Table 1. Solubility of active ingredients in dissolution media at 37°C

Permeability:

Based on the extent of absorption in humans observed in [^{14}C]-labeled mass balance studies, olanzapine and samidorphan are "lowly permeable" drug substances. Note that the Applicant claimed at least (b) (4)% of the administered dose was estimated to be absorbed based on radioactivity excreted in urine and metabolites detected in fecal samples). However, both olanzapine and samidorphan demonstrated were reported to have high permeability in the Caco-2 cells and were stable in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). Note that the Applicant claimed apical-to-basolateral apparent permeabilities of both drug substances were greater than that of co-incubated minoxidil (high permeability marker) in Caco-2 cell system. After oral administration (b) (4)% of the administered dose of olanzapine was estimated to be absorbed based on radioactivity samples. The absolute oral BA of samidorphan was 69%.

Dissolution:

The proposed olanzapine and samidorphan tablets, 5/10, 10/10, 15/10, 20/10 mg/mg, are rapidly dissolving within 30 minutes when using the proposed dissolution method (see B.2).

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***Adequate***

Dissolution Method Development

The dissolution conditions, apparatus 2 with sinker, agitation speed of 75 rpm, and 500 mL of 0.1N HCl as dissolution medium were considered acceptable for the dissolution testing of the proposed drug products at batch release and on stability.

Selection of Dissolution Medium:
Based on the USP monograph for olanzapine tablets as well as the FDA guidance for immediate release dosage forms, the Applicant selected dissolution medium 0.1N HCl for the drug product dissolution test. Note that solubility of olanzapine and samidorphan L-malate is (b) (4) mg/mL and > (b) (4) mg, respectively, in 0.1 N HCl at 37 °C, (b) (4) dissolution volume of 500 mL was selected (b) (4) dissolution at 30 minutes was achieved for the 5/10, 10/10, 15/10, 20/10 mg/mg tablets in 0.1N HCl.

Selection of Apparatus and Paddle Speed:
USP Apparatus 2 at 75 rpm was selected for the drug product dissolution method based on the USP monograph dissolution method for olanzapine tablets. A three-prong sinker added to the dissolution tests (b) (4)

Initially, a paddle speeds of (b) (4) rpm and 75 rpm were evaluated using a (b) (4) mL vessel volume to align with the USP monograph for olanzapine tablets. It was observed that the use of (b) (4) rpm in a (b) (4) mL vessel volume (b) (4) (b) (4) compared to 75 rpm (Figure 1).

Figure 1: Comparison of Paddle Speed in (b) (4) mL (n=6)

Selection of Vessel Volume:
The 500 and (b) (4) mL vessel volumes were initially evaluated with paddle speed of 75 rpm and were found to result in similar dissolution profiles of (b) (4) development tablets (Figure 2). Therefore, 500 mL vessel volume was selected.

Figure 2: Comparison of Media Volume at 75 rpm (n=6)

(b) (4)

Discriminating Ability of Dissolution Method:

The Applicant identified the rate limiting step (b) (4) (b) (4) hence the focus in their investigation for discriminating ability of the proposed dissolution method.

(b) (4)

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Validation of Dissolution method: ***Adequate***

The dissolution method validation was carried out by two analysts. The results show specificity, linearity, range, accuracy, precision, and robustness are acceptable (see Appendix 2).

Dissolution Acceptance criterion:

Based on the totality of dissolution data from the clinical batches and the to-be-marketed batch, this Reviewer determined that the proposed dissolution acceptance criterion of "NLT (b) (4)% (Q) in 30 minutes" for batch release and stability testing is acceptable.

B.3 BIOPHARMACEUTICS RISK ASSESSMENT

The drug substance, olanzapine and samidorphan are considered by the Applicant to be a BCS class 3, high solubility and low permeability drug. Thus, the risk in dissolution is low. In addition, (b) (4) is not considered critical regarding treatment effect or disease control for the proposed indication.

B.4 BRIDGING OF FORMULATIONS

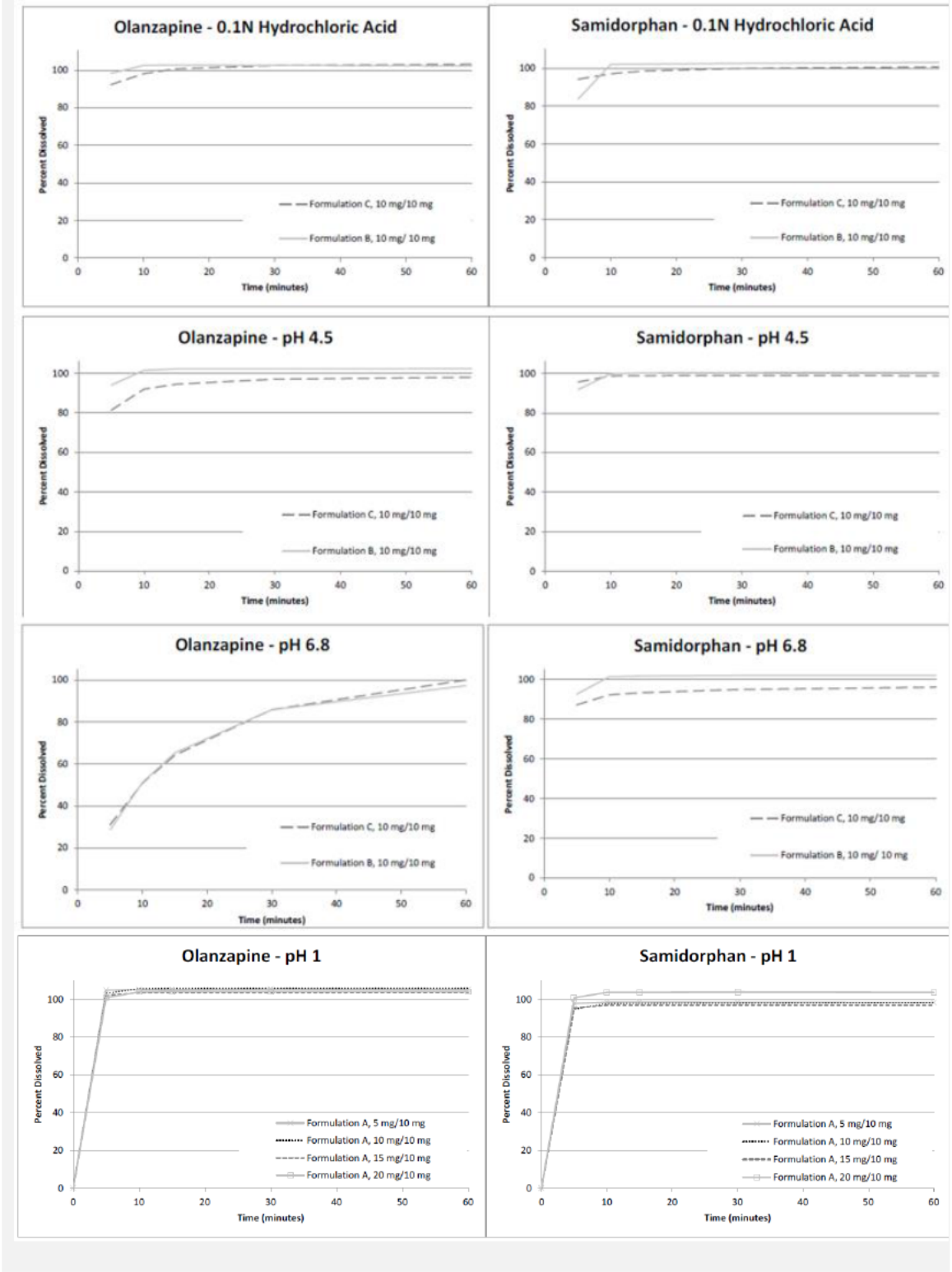
Assessment: ***Adequate***

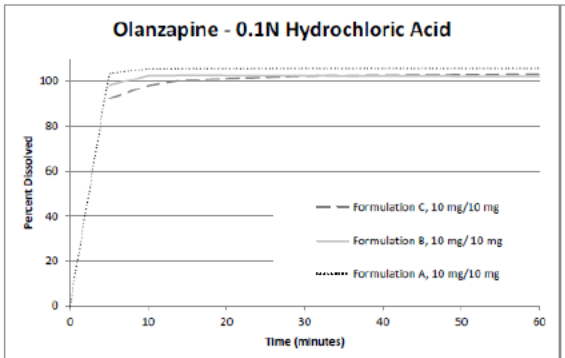
Three formulations were used during clinical development, designated as Formulations A (to-be-marketed), B and C (see Appendix 1). All formulation compositions contained the same ingredients (b) (4)

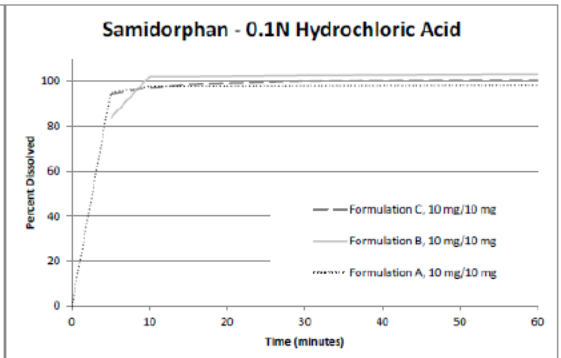
(b) (4)

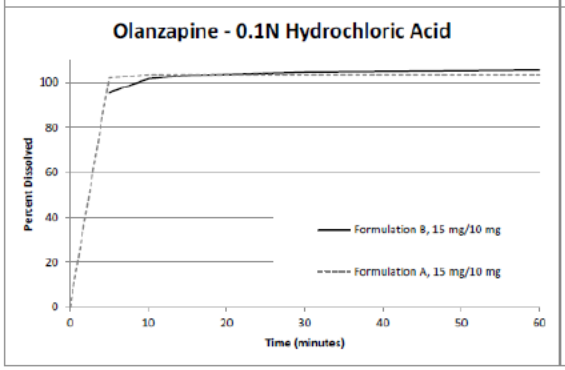
(b) (4) Bridging among the formulations were established using multi-media dissolution tests with 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer as dissolution medium, as per the principle and recommendations in SUPAC Guidance (see Figure 9 and Appendix 1).

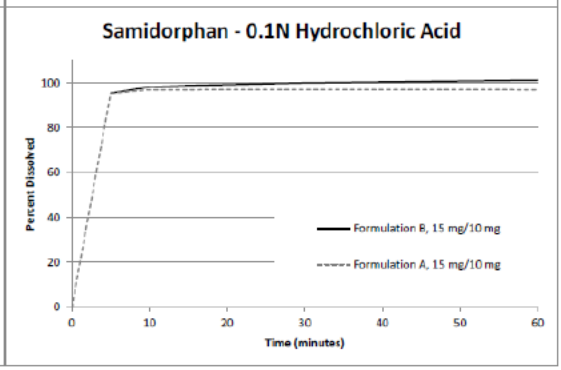
Figure 9. Bridging Throughout Product Development

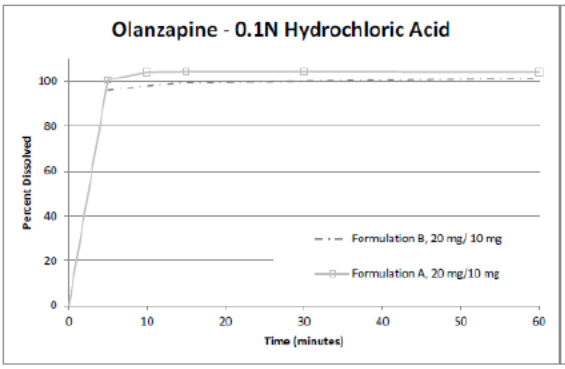

Olanzapine - 0.1N Hydrochloric Acid
Percent Dissolved
Time (minutes)
Formulation C, 10 mg/10 mg
Formulation B, 10 mg/ 10 mg
Samidorphan - 0.1N Hydrochloric Acid
Percent Dissolved
Time (minutes)
Formulation C, 10 mg/10 mg
Formulation B, 10 mg/10 mg
Olanzapine - pH 4.5
Percent Dissolved
Time (minutes)
Formulation C, 10 mg/10 mg
Formulation B, 10 mg/10 mg
Samidorphan - pH 4.5
Percent Dissolved
Time (minutes)
Formulation C, 10 mg/10 mg
Formulation B, 10 mg/10 mg
Olanzapine - pH 6.8
Percent Dissolved
Time (minutes)
Formulation C, 10 mg/10 mg
Formulation B, 10 mg/10 mg
Samidorphan - pH 6.8
Percent Dissolved
Time (minutes)
Formulation C, 10 mg/10 mg
Formulation B, 10 mg/ 10 mg
Olanzapine - pH 1
Percent Dissolved
Time (minutes)
Formulation A, 5 mg/10 mg
Formulation A, 10 mg/10 mg
Formulation A, 15 mg/10 mg
Formulation A, 20 mg/10 mg
Samidorphan - pH 1
Percent Dissolved
Time (minutes)
Formulation A, 5 mg/10 mg
Formulation A, 10 mg/10 mg
Formulation A, 15 mg/10 mg
Formulation A, 20 mg/10 mg

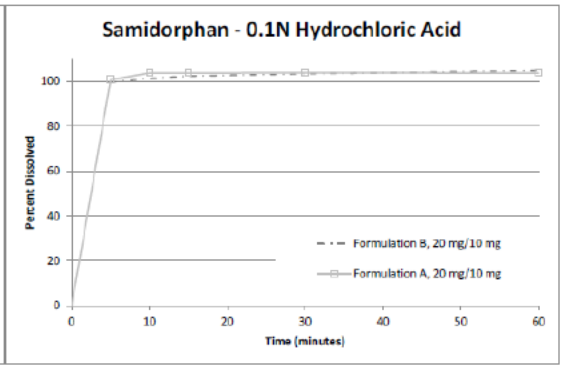

Olanzapine - 0.1N Hydrochloric Acid
Percent Dissolved
Time (minutes)
Formulation C, 10 mg/10 mg
Formulation B, 10 mg/ 10 mg
Formulation A, 10 mg/10 mg


Samidorphan - 0.1N Hydrochloric Acid
Percent Dissolved
Time (minutes)
Formulation C, 10 mg/10 mg
Formulation B, 10 mg/10 mg
Formulation A, 10 mg/10 mg


Olanzapine - 0.1N Hydrochloric Acid
Percent Dissolved
Time (minutes)
Formulation B, 15 mg/10 mg
Formulation A, 15 mg/10 mg


Samidorphan - 0.1N Hydrochloric Acid
Percent Dissolved
Time (minutes)
Formulation B, 15 mg/10 mg
Formulation A, 15 mg/10 mg


Olanzapine - 0.1N Hydrochloric Acid
Percent Dissolved
Time (minutes)
Formulation B, 20 mg/ 10 mg
Formulation A, 20 mg/10 mg


Samidorphan - 0.1N Hydrochloric Acid
Percent Dissolved
Time (minutes)
Formulation B, 20 mg/10 mg
Formulation A, 20 mg/10 mg

APPENDIX 1: Proposed Formulations

Particle Size Distribution

Process Capabilities	Particle Size Distribution (µm)		
	Dv[10]	Dv[50]	Dv[90]
Minimum	(b) (4)		
Maximum			
Mean			
Standard Deviation (SD)			
Standard Deviation × 3			
Mean + 3(SD)			
Mean - 3(SD)			

Batch	Approx. Batch size	Particle Size Distribution (µm)		
		Dv[10]	Dv[50]	Dv[90]
OLZTFA000515	(b) (4)			
OLZTFA000615				
OLZTFA000715				
OLZTFA000815				
OLZTFA000915				
OLZTFA001015				
OLZTFA001115				
OLZTFA001215				
OLZTFA001316				
OLZTFA001416				
OLZTFA001516				

Batch	Dv_{10} µm	Dv_{50} µm	Dv_{90} µm
0000045274	(b) (4)		
0000045275			
0000045276			
0000049586			
0000049587			
0000049588			

Formulation Compositions:

5 mg/10 mg Tablets

Component	Quality Standard	Amount (mg) per tablet	Amount (%wt) per coated tablet
Olanzapine	USP	5.00[a]	(b) (4)
Samidorphan L-malate	In-House Standard	13.62[a]	
Microcrystalline cellulose	NF		(b) (4
Lactose monohydrate	NF		
Crospovidone	NF		
Colloidal silicon dioxide	NF		
Magnesium stearate	NF		
			(b) (4)

10 mg/10 mg Tablets

Component	Quality Standard	Amount (mg) per tablet	Amount (%wt) per coated tablet
Olanzapine	USP	10.00[a]	(b) (4)
Samidorphan L-malate	In-House Standard	13.62[a]	
Microcrystalline cellulose	NF		(b) (4
Lactose monohydrate	NF		
Crospovidone	NF		
Colloidal silicon dioxide	NF		
Magnesium stearate	NF		
			(b) (4)

15 mg/10 mg Tablets

Component	Quality Standard	Amount (mg) per tablet	Amount (%wt) per coated tablet
Olanzapine	USP	15.00[a]	(b) (4)
Samidorphan L-malate	In-House Standard	13.62[a]	
Microcrystalline cellulose	NF		(b) (4
Lactose monohydrate	NF		
Crospovidone	NF		
Colloidal silicon dioxide	NF		
Magnesium stearate	NF		
			(b) (4)

20 mg/10 mg Tablets

Component	Quality Standard	Amount (mg) per tablet	Amount (%wt) per coated tablet
Olanzapine	USP	20.00[a]	(b) (4)
Samidorphan L-malate	In-House Standard	13.62[a]	
Microcrystalline cellulose	NF		(b) (4
Lactose monohydrate	NF		
Crospovidone	NF		
Colloidal silicon dioxide	NF		
Magnesium stearate	NF		
			(b) (4)

Formulations Throughout Drug Development:

Tablet Strength (OLZ mg/ SAM mg)	Component	Formulation C	Formulation B	Formulation A
		Amount Per Coated Tablet – mg (% wt/wt)		
5/10				(b) (4)
10/10				
15/10				
20/10				

Abbreviations: (b) (4) NA=not applicable

To-be marketed formulation (A)

Function Component	Tablet Strength (OLZ/SAM) 5 mg/10 mg	10 mg/10 mg	15 mg/10 mg	20 mg/10 mg
	Amount per Coated Tablet, mg (% wt/wt)			
Drug Substance				
OLZ	5.00 (b) (4)	10.00 (b) (4)	15.00 (b) (4)	20.00 (b) (4)
SAM L-malate	13.62	13.62	13.62	13.62
				(b) (4)

Abbreviations: NF=National Formulary; OLZ=olanzapine; SAM=samidorphan.

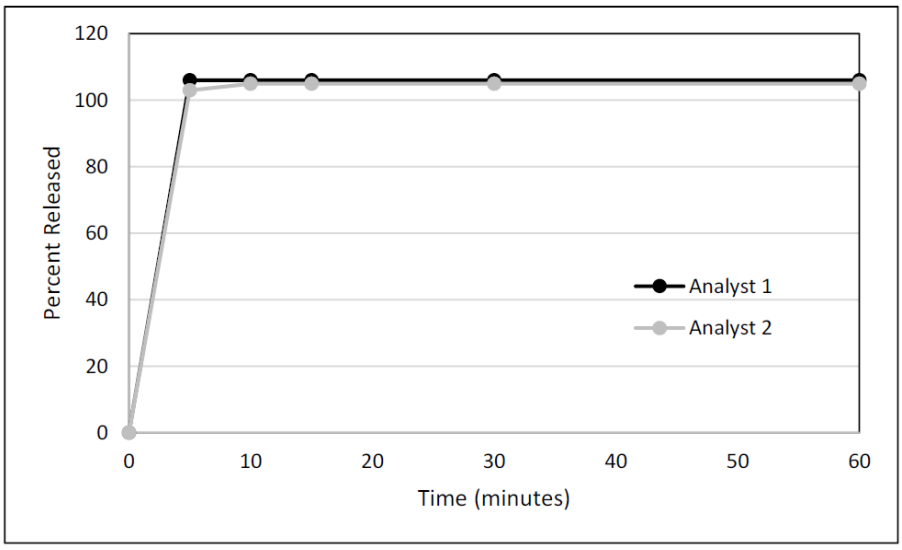
APPENDIX 2: Validation of Dissolution method

Intermediate Precision		5 mg/10 mg		20 mg/10 mg	
		Olanzapine	Samidorphan	Olanzapine	Samidorphan
Analyst 1 (n=12)	Mean % Released	106	98	105	96
	% RSD	3	2	3	3
Analyst 2 (n=12)	Mean % Released	105	99	106	96
	% RSD	4	2	1	2
Pooled % RSD		3	2	2	3
Pooled % RSD Acceptance Criterion		(b) (4)			
Absolute Difference - %		1	1	1	0
Absolute Difference Acceptance Criterion		(b) (4)			

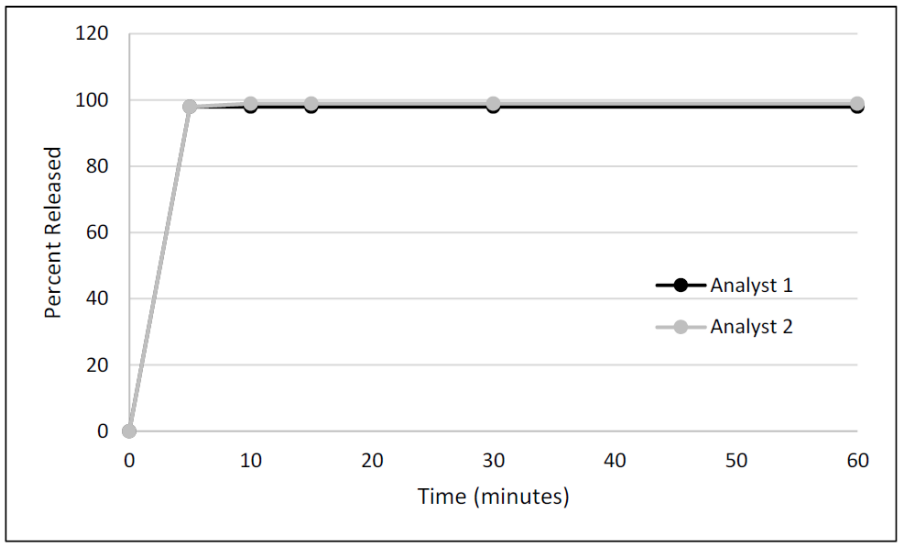
Parameter	Acceptance Criteria	Result
Specificity		(b) (4)
Linearity		
Repeatability		
Intermediate Precision		
Accuracy		
Range		

Robustness - Standard Solution Stability	(b) (4)
Robustness - Sample Solution Stability	
Robustness - Dissolution Parameters	
Robustness - Standard Solution Stability	
Robustness - Sample Solution Stability	
Robustness - Dissolution Parameters	

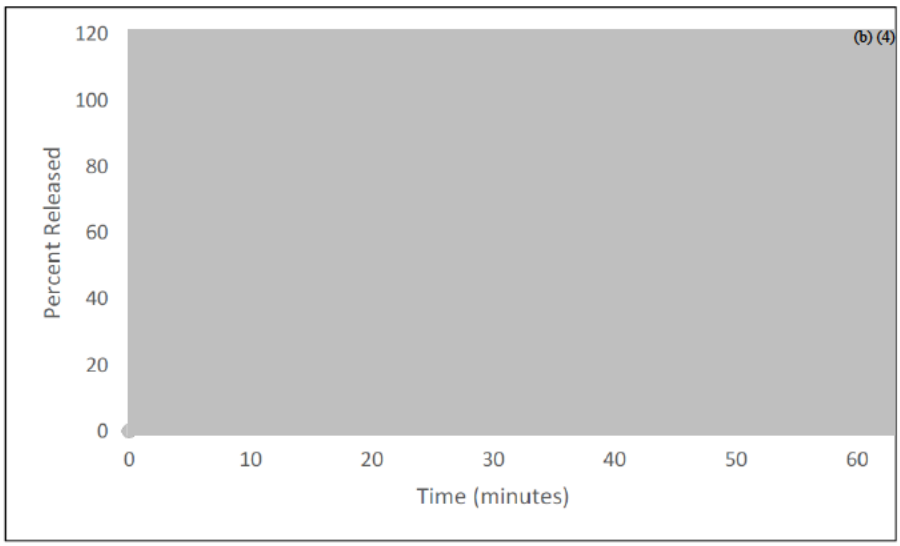
Olanzapine 5mg/10 mg



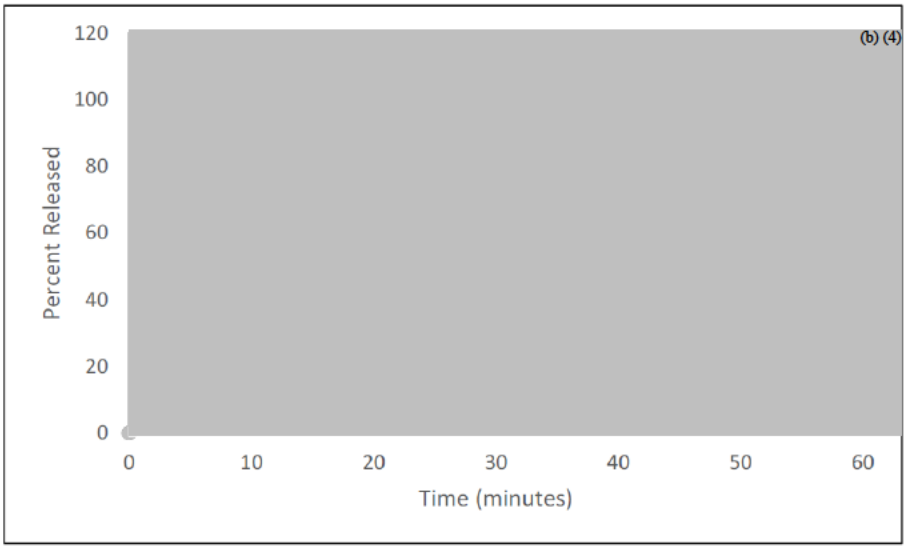
Samidorpfan 5mg/10 mg



Olanzapine 20mg/10 mg



Samidorpfan 20mg/10 mg



Assadollah Noory

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Comments: Hi Ta-Chen, Would you like to approve this document? Thanks, Assad

Ta-Chen Wu

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Valerie Amspacher

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