CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212895Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 212895: Levamlodipine Maleate Tablet

OPQ Integrated Quality Review

Recommendation: Recommended for Approval

Drug Name/Dosage Form	Levamlodipine Maleate Tablets
Strength	1.25mg, 2.5mg, and 5mg
Route of Administration	Tablets for oral use
Indication	For the treatment of hypertension in the US (one of the indications approved for the listed drug and generic amlodipine products). To be used alone or in combination with other antihypertensive and antianginal agents for the treatment of hypertension
Rx/OTC Dispensed	Rx
Applicant	CSPC Pharmaceutical Group
US agent, if applicable	N/A
Submissions (s) Reviewed	NDA 212895, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Kabir Shahjahan	ONDP/DNDAPI/NDBI
Drug Product, Labeling, and Environmental Assessment (EA)	Mariappan Chelliah	ONDP/DNDPI/NDPBI
Process and Facility	Ruth Moore	OPF/DPAI/PABI
Biopharmaceutics	Om Anand	ONDP/DB/BBI
Regulatory Business Process Manager	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

1. RELATED/SUPPORTING DOCUMENTS:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
DMF	Type II DMF (b) (4)	Reviewed and found adequate

2. CONSULTS:

None.

(Continued on next pages)

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 212895 Levamlodipine Maleate Tablet is recommended for approval. As part of this action, an expiration period of 24 months for the product, when stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) in the commercial packaging, is granted.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

II. Summary of Quality Assessments

The applicant, Ouyi Pharmaceutical Co, has sought U.S. marketing approval for Levoamlodipine Maleate Tablet under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act. The non-proprietary name approved by the USAN Council is "levamlodipine". Therefore, the name "levamlodipine" is used instead of (b) (4) throughout this review. Levamlodipine is the enantiomer-resolved (S)-amlodipine and pharmacologically active enantiomer in amlodipine. The listed drug (LD) NORVASC® of Pfizer Inc., approved by the Agency in 1992 (NDA 019787) is a 1:1 racemic mixture of levamlodipine and dextroamlodipine. The proposed product is indicated for the treatment of hypertension in the US (one of the indications approved for the LD and generic amlodipine products). During the past 15 years, Levamlodipine Maleate tablet has been widely used for the treatment of hypertension in adults in China. The proposed dosage strengths to-be-marketed in the US are 1.25, 2.5 and 5 mg Levamlodipine tablets, (b) (4) (b) (4) From the quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, and stability.

A. Drug Substance Quality Summary

The drug substance levamlodipine maleate, a crystalline powder, is the maleate salt of (S)-enantiomer of amlodipine base (b) (4) The CMC information concerning the structural characterization, manufacturing process and release specification is acceptable. Specifically, the commercial manufacturing process (b) (4) has been reviewed and found adequate. (b) (4) The

identified critical process parameters are adequate. No impurity levels in the drug substance exceed the ICH Q3A qualification threshold.

Controls of residual solvents, elemental impurities, and mutagenic impurities comply with applicable ICH guidances. The batch analysis data of 3 commercial drug substance batches conform to the proposed specification. The optical purity of the drug substance is controlled (b) (4) The key analytical methods including HPLC methods for assay, related substance, (b) (4) impurity, (b) (4) content and (b) (4) residual solvents, as well as particle size distribution (in-house) are adequate and validated. The (b) (4) impurity of the drug substance is monitored as (b) (4) with a limit of (b) (4) %, (b) (4) Stability data support a retest period of (b) (4) months for levamlodipine maleate per ICH Q1E (R2).

B. Drug Product Quality Summary

B.1. Product Design, and Release Specification: Levamlodipine tablet is to be marketed in three different strengths: 1.25 mg, 2.5 mg, and 5 mg. The LD (amlodipine besylate) is available as 2.5 mg, 5 mg, 10 mg tablets. While amlodipine besylate is a racemic mixture, the proposed product contains only the pharmacologically active (S) enantiomer. Accordingly, only half the amount of the active ingredient is required in each tablet to reach the same therapeutic efficacy as the LD. The proposed 2.5 mg and 5 mg tablets contain functional scoring, which is unnecessary. (b) (4) All the excipients used in the formulation are of compendial grade and their respective maximum daily exposures are considered qualified. The product release specification, involving testing of all the product critical quality attributes (CQAs), is adequate to ensure the assure the identity, strength, quality, purity, potency and batch-to-batch consistency through the product's lifecycle. The controls for impurities meet the USP monograph for amlodipine besylate tablets or ICH Q3B guidance. All the non-compendial analytical methods have been adequately validated. The batch data demonstrate that the applicant can manufacture the tablets with a consistent quality that meets the specification. Levamlodipine tablets are packaged either as 90-count in 40-cc HDPE bottles or 500-count in 200-cc HDPE bottles. The applicant has performed a risk assessment screening for elemental impurities, per ICH Q3D, taking into account any potential contributions from the drug substance, excipients, manufacturing equipment and process, and leachables from the container closure system. Based on this assessment, the elemental impurities in the proposed product do not exceed the ICH Q3D-compliant permitted daily exposure (PDE) limits. Hence, no release testing for elemental impurities is required.

B.2. Manufacturing: Briefly, the manufacturing process involves (b) (4)

(b) (4)

The commercial batch formula reflects the proposed composition and is consistent with the proposed commercial batch records.

B.3. Microbiological Aspects: The proposed drug product is a non-sterile tablet. The microbiological testing is included in release and stability specifications. Testing performed per USP <61> and <62> is adequate for the proposed product. Based on stability studies, all stability batches meet the product specification for microbiological testing.

B.4. Biopharmaceutics Aspects: The application relies on the Agency's previous finding of safety and efficacy of the listed drug (LD) product, NORVASC® Tablets (amlodipine besylate, NDA 019787). The Biopharmaceutics review evaluated the: i) *in vitro* dissolution method and acceptance criterion for the proposed drug product, and ii) biowaiver request for lower strength (1.25mg) tablet.

In Vitro Dissolution Testing of the Finished Product: The method has been validated for system suitability, specificity, precision, linearity, accuracy, (b) (4) robustness and solution stability. (b) (4)

The proposed dissolution method (i.e. US Apparatus II (Paddle) at 75 rpm using 500 mL 0.01 N HCl; Q= (b) (4) % in (b) (4) minutes) is acceptable for the QC of the proposed drug product. The applicant has adequately demonstrated the suitability of the dissolution method for batch release and stability testing.

Biowaiver for Lower Strength: The applicant's biowaiver request for the lower strength (1.25 mg) is justified and acceptable mainly because the: a) tablets represent the same dosage form but in different strengths, b) three strength tablets are identical. (b) (4)

(b) (4)

c)

(b) (4) d) BE study [LAM-US-101] was been found acceptable by the Clinical Pharmacology review team, and e) *in-vitro* dissolution comparability of the 5 mg and 2.5 mg tablet strengths to the 1.5 mg tablet batches has been demonstrated.

B.5. Container Closure System: The applicant proposes to market the drug product in two configurations i.e., a) 90-count in 40-cc HDPE bottles (all strengths), and b) 500-count in 200-cc HDPE bottles (all strengths). The components of the proposed container closure system meet appropriate regulations and are suitable for packaging the drug product. Furthermore, available stability data suggest that the container closure systems

are expected to provide adequate protection for the tablets through the proposed shelf-life.

B.6. Stability, Storage Conditions and Expiration Date:

The applicant has provided 6 months of accelerated and 12 months long-term stability data corresponding to 3 batches per strength, per packaging configuration. Other than some data fluctuation for the water content, no trending is noted under both the storage conditions. The proposed shelf-life of 24 months, when stored at controlled room temperature of 20°C to 25°C (68°F to 77°F), is acceptable.

C. Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended an overall approval for all the currently listed manufacturing facilities concerning this NDA.

D. Environmental Assessment: The applicant's claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) on the basis that the estimated concentration of the product at the point of entry into the aquatic environment will be well below 1 part per billion, is acceptable

E. Any Special Product Quality Labeling Recommendations:

N/A

F. Life Cycle Knowledge Information

See Final Risk Assessment on the next page.

Final Risk Assessment

Levamlodipine Maleate Tablet

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay, Stability	• Formulation • Container closure • Impurity exceeding specification • Process parameters • Scale/ equipment/ site	Low (L)	(b) (4)	Acceptable	
(b) (4)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Mode-rate (M)		Acceptable	N/A

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Content Uniformity	• Formulation • Particle size • Segregation • Raw materials • Process parameters • Scale/ equipment/ site	Moder-ate (M)	(b) (4)	Acceptable	The applicant has committed that (b) (4)
(b) (4)	• Formulation • Process parameters • Scale/equip ment/site	Low (L)		Acceptable	
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equip ment/site • API sources	Moder-ate (M)		Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters Scale/equip ment/site	Low (L)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 212895 Levamlodipine Maleate Tablet is recommended for approval. As part of this action, an expiration period of 24 months for the product, when stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) in the commercial packaging, is granted.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products
ONDP/DNDPI/NDPB

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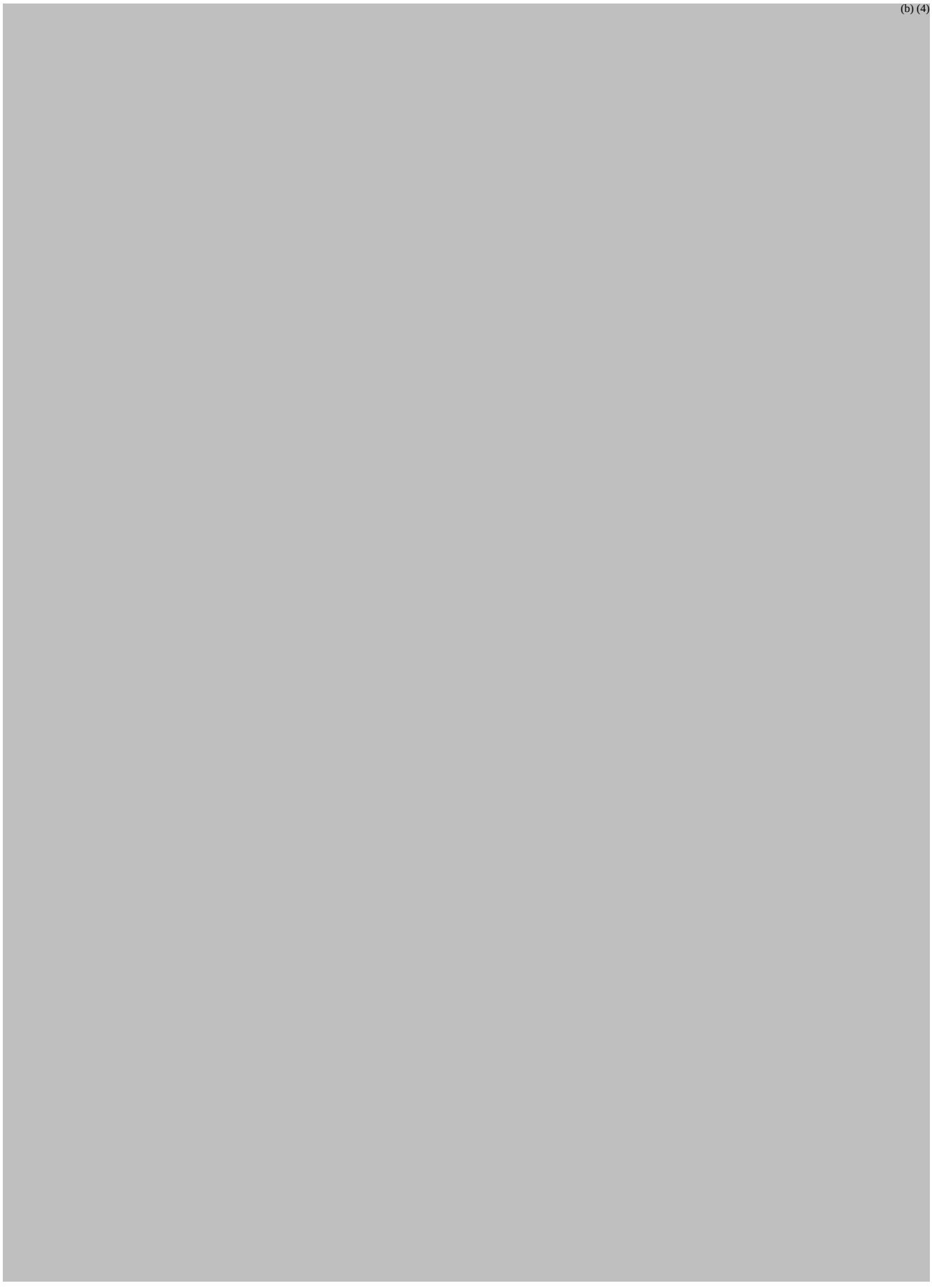
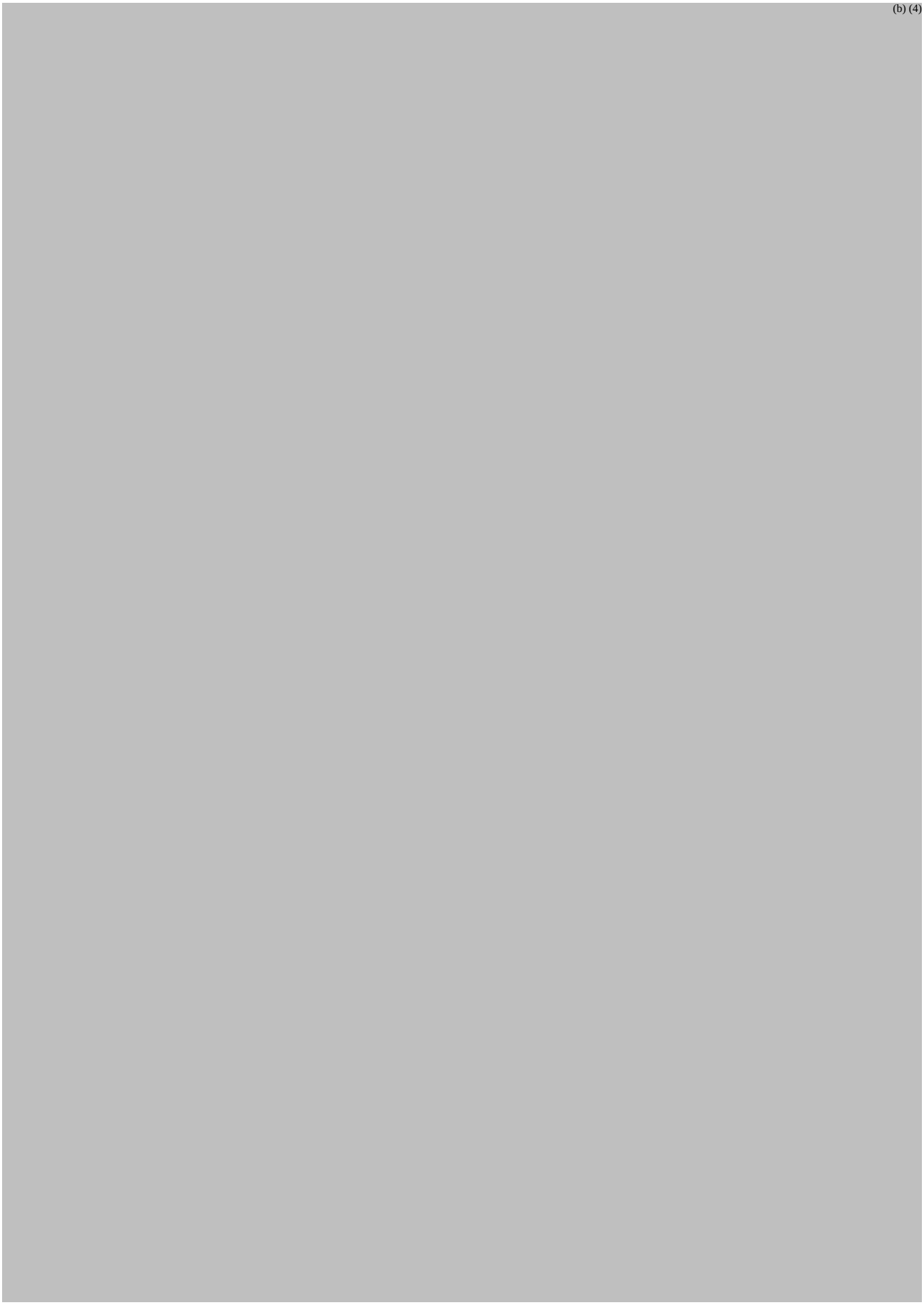
(b) (4)




(b) (4)

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate, but non-proprietary name is pending approval by USAN.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME	pending
Established name(s)	(b) (4)	pending
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 1.25 mg, 2.5 mg (functionally scored), and 5 mg (functionally scored).	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	2.5 mg and 5 mg tablets are functionally scored.	Adequate
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	1.25 mg, 2.5 mg, 5 mg	adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Strength is expressed on neutral molecule basis	adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Includes identifying characteristics	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate data provided to support the functional scoring of 2.5 mg and 5 mg tablets.	adequate
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)	TRADENAME (b) (4)	pending
Dosage form(s) and route(s) of administration	Dosage: tablet ROA: oral	adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Edited to include equivalent statement	adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Edited to list the excipients alphabetically	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	Calcium channel blocker	adequate
Chemical name, structural formula, molecular weight	All are included	adequate
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa or pH)	Appearance is included	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	1.25, 2.5, 5 mg	adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 90 or 500 tablets	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Appearance, shape and engraving are included	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate data provided to support the functional scoring on the 2.5 mg and 5 mg tablets	adequate
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.)	Dispense in tight, light-resistant containers (USP).	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."	n/a	n/a
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Edited as: Store bottles at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	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	Labeling includes child resistant statement.	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	CSPC Ouyi Pharmaceutical Co., Ltd.	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

(b) (4)

3.2 Carton Labeling

Not applicable

Item	Information Provided in the NDA	Assessor's Comments about Container Labeling
Proprietary name, established name, and dosage form (font size and prominence	TRADENAME (b) (4) tablets	Adequate
Dosage strength	1.25 mg; 2.5 mg; 5 mg	adequate
Route of administration	none	ROA not required for oral use. Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains 1.25 mg (b) (4) (equivalent to 1.6 mg (b) (4))	adequate
Net contents (e.g. tablet count)	90 or 500 tablets	adequate
"Rx only" displayed on the principal display	Yes	adequate
NDC number	1.25 mg: 24075-410-09 (90 ct); 24075-410-50 (500 ct) 2.5 mg: 24075-411-09 (90 ct); 24075-411-50 (500 ct) 5 mg: 24075-412-09 (90 ct); 24075-412-50 (500 ct)	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.	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].	adequate
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		

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured by: CSPC Ouyi Pharmaceutical Co., Ltd. Shijiazhuang, Hebei, China, 052160	adequate
Medication Guide (if applicable)	n/a	n/a
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

The container and PI labels have been edited to meet the appropriate regulations. However, the Applicant applied for the non-proprietary name only during the review cycle. Per Dr. David Lewis, FDA representative for USAN Council, the non-proprietary name "levamlodipine maleate" is expected to be approved by the USAN council by the end of Oct, 2019.

Please note that current labeling list the non-proprietary name as (b) (4) which differs slightly from the name "levamlodipine" expected to be approved the USAN Council. The labeling will be edited to reflect this change.

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan Chelliah

Secondary Assessor Name: Wendy Wilson-Lee

Mariappan Chelliah

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Wendy Wilson- Lee

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(b) (4)

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BIOPHARMACEUTICS

NDA: 212895(505(b)(2))

Drug Product Name / Strength: Levoamlodipine Maleate Tablets, 1.25, 2.5 and 5 mg

Route of Administration: Oral

Applicant Name: CSPC Ouyi Pharmaceutical Co., Ltd.

Indication: Treatment of hypertension

Review Summary:
This 505 (b) (2) submission is for Levoamlodipine Maleate, the enantiomer S of amlodipine. The application relies on the Agency's previous finding of safety and efficacy of the listed drug (LD) product, NORVASC® Tablets (amlodipine besylate, NDA 019787). The 2.5 and 5 mg strengths of the test product were used in the bioequivalences (BE) studies, 73912 (pilot) and LAM-US-101 (pivotal), respectively. The pivotal bioavailability and food effect study is the basis to bridge the proposed drug product to the LD.

This review evaluates the proposed dissolution method, the dissolution acceptance criterion, and the biowaiver request.

Dissolution method and acceptance criterion: ACCEPTABLE

The following proposed dissolution method and revised acceptance criterion are acceptable:

Dissolution Method and Acceptance Criterion	
Apparatus	USP II (Paddle)
Rotation Speed	75 RPM
Medium	0.01 N HCl
Volume	500 mL
Acceptance Criterion	Q= (b)(4)% at 20 minutes

Biowaiver Request: ACCEPTABLE

The Applicant's biowaiver request for the lower strength (1.25 mg) is granted.

List of Submissions being reviewed: Original (2/28/2019) and IR Responses (08/19/2019 and 10/21/2019)

Review Recommendation:
Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212895 for Levoamlodipine Maleate Tablets, 1.25, 2.5 and 5 mg, is recommended for APPROVAL.

Primary Biopharmaceutics Reviewer: Zhuojun Joan Zhao, Ph.D.
Secondary Reviewer: Om Anand Ph.D. for Jing Li, Ph.D.

Background:

Levoamlodipine maleate is the pharmacologically active enantiomer of racemic amlodipine. The proposed drug product is a purified (S)- Amlodipine Tablet. The Applicant submitted a bioavailability study comparing the proposed drug product, (S)-Amlodipine Tablets 5 mg to the LD, NORVASC ® (amlodipine besylate) Tablets 10 mg (a racemic mixture of (S) and (R) amlodipine, NDA 019787) in health subjects and proposes to rely on the FDA's previous finding of safety and efficacy of the LD product, NORVASC® Tablets.

Drug Substance

The drug substance, levoamlodipine maleate, (b) (4)

BCS Designation

The Applicant does not request an official BCS designation, however levoamlodipine maleate is considered as a drug substance with high solubility based on the Biopharmaceutical Classification System (BCS).

Drug Substance Solubility:

The Applicant found that the drug substance, levoamlodipine maleate, has high aqueous solubility across the physiological pH range, as shown below:

Table 1: Aqueous solubility of levoamlodipine maleate in various pH media(37°C)

Media	Solubility (mg/mL)
pH1.2	104.981
pH2.0	43.700
pH3.4	15.056
pH4.1	31.484
pH4.5	33.075
pH5.5	37.929
pH6.0	39.117
pH6.8	35.746
Water	30.096
pH7.4	32.463
pH8.0	31.609

Formulation:

The proposed Levoamlodipine Maleate Tablet is an immediate release tablet. All three strength Levoamlodipine Maleate Tablets are identical (b) (4) The composition of the proposed drug product is provided in Table 2.

Table 2: Qualitative composition of Levoamlodipine Maleate Tablets

Component	Standard	Function	Theoretical Weight/Tablet (mg); % (W/W)		
			1.25 mg	2.5 mg	5 mg
Levoamlodipine maleate	In-house	API	*1.6045 (b) (4)	*3.209 (b) (4)	*6.418 (b) (4)
Betadex	NF				(b) (4)
Pregelatinized starch (b) (4)	NF				
Microcrystalline cellulose (b) (4)	NF				
Colloidal silicon dioxide (b) (4)	NF				
Magnesium stearate	NF				
Total tablet weight					

**1.6045 mg of levoamlodipine maleate equals to 1.25 mg of levoamlodipine; 3.209 mg of levoamlodipine maleate equals to 2.5 mg of levoamlodipine; 6.418 mg of levoamlodipine maleate equals to 5 mg of Levoamlodipine.*

Dissolution Method:

The proposed dissolution method is based on the dissolution method described in the FDA-Database dissolution method for amlodipine besylate tablets:

Proposed Dissolution method	
Apparatus	USP II (Paddle)
Rotation (rpm)	75
Medium	0.01 N HCl
Volume (mL)	500 mL

In the Dissolution Development Report (Module 3.2.P.2), justification for the choice of dissolution parameters are provided and summarized below.

(b) (4)

(b) (4)

Reviewer Assessment: Acceptable
Based on the Applicant's provided information the selection of the dissolution conditions is acceptable.

Dissolution Method Validation:

(b) (4)

Discriminating Power of the Method:

(b) (4)

(b) (4)

Dissolution Acceptance Criterion:

The Applicant originally proposed a dissolution acceptance criterion of Q= (b) (4)% in (b) (4)minutes.

(b) (4)

(b) (4)

[redacted]

Biowaiver:

The proposed Levoamlodipine Maleate Tablet is developed in three strengths, 1.25, 2.5 and 5 mg. The 2.5 and 5 mg strengths of the test product were used in the bioequivalences BE studies, 73912 (pilot) and LAM-US-101 (pivotal), respectively. The Applicant is requesting a biowaiver for the 1.25 mg strength based on the similar composition to the 5 mg tablets and the similar in vitro dissolution profile.

Reviewer's Assessment of the Biowaiver Request: ACCEPTABLE

The Applicant's biowaiver request for the lower strength (1.25 mg) of Levoamlodipine Maleate Tablets is justified and acceptable.

- The drug products are in the same dosage form but in different strengths.
- The formulation composition is provided in Table 2. All three strength Levoamlodipine Maleate tablets are identical. (b) (4)

- (b) (4)
- The BE study [LAM-US-101] was found acceptable by OCP reviewer Dr. Venkateswaran ChithambaramPillai, which is the basis for the bridging of the proposed Levoamlodipine Maleate Tablet to the LD.
- The in-vitro dissolution comparability of the 5 mg and 2.5 mg tablet strengths to the 1.5 mg tablet batches respectively have been demonstrated (Figure 1 and Table 4).

APPENDIX 1: *Biopharmaceutics Information Request Dated August 12, 2019 and the Applicant's response on August 19, 2019*

1. Based on the submitted dissolution data, a dissolution acceptance criterion of Q= (b)(4) in (b)(4) minutes for your proposed Levoamlodipine Maleate Tablets, 1.25, 2.5 and 5 mg is recommended. Please update your drug product release and stability specifications accordingly.

In addition, please be advised, that all proposed registration batches are expected to meet the revised dissolution acceptance criterion in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

Applicant's Response to Biopharmaceutics Comment:

Since levoamlodipine maleate is being developed as an immediate release tablet with high solubility, per the FDA Guidance entitled "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances, August 2018", a dissolution acceptance criterion assessed at (b)(4) min is considered in conformance with the guidance. As such, all currently available dissolution data were tested only at (b)(4) minutes. The data available so far indicate adequate dissolution at (b)(4) min (summarized below). We have no dissolution data at (b)(4) minutes to support the Agency's proposed (b)(4)% (Q) at (b)(4) minutes dissolution acceptance criterion.

(b)(4)

Reviewer Note:

The Applicant's proposed (b)(4) is not accepable. Based on the data in the submission, the Applicant will be requested to revise the dissolution acceptance criterion (Appendix 2).

APPENDIX 2: *Biopharmaceutics Information Request Dated October 17, 2019 and the Applicant's response on October 21, 2019*

1. *We reviewed your response dated August 19, 2019, including your proposal* (b) (4) *However, your proposed* (b) (4) *r proposal* (b) (4) *is not acceptable. Please note that your proposed* (b) (4) (b) (4) (b) (4) *is considered permissive and not acceptable.*

   Based on the totality of information available, including submitted dissolution data a new dissolution acceptance criterion of Q= (b) (4) *% in 20 minutes is recommended for your proposed Levoamlodipine Maleate Tablets, 1.25, 2.5 and 5 mg. Please update your drug product release and stability specifications accordingly.*

2. *Please submit complete dissolution profiles using the currently available long-term stability batches, including the clinical and the and the exhibit batches. Collect samples (N=12) at 5, 10, 15, 20 and 30 minutes, and report individual unit data, means, ranges and graphic presentation for the mean dissolution data for each profile. Indicate the age of the batch at the time of dissolution testing.*

Applicant's Response to Biopharmaceutics Comment 1:

We accept the Agency's recommendation for dissolution acceptance criterion of Q = (b) (4) % in 20 minutes. The drug product release (Module 3.2.P.5.1), analytical procedure (Module 3.2.P.5.2), and stability protocols (containing stability specifications, in Module 3.2.P.8) have been revised to reflect the new dissolution acceptance criterion.

Reviewer Note:
The Applicant's response is satisfactory.

Applicant's Response to Biopharmaceutics Comment 2:

The required dissolution profiles of three batches (B48180101, B48180102, and B48180103) are provided as appendix to this response document. Of note, Batch B48180102 5 mg tablets were used in the pivotal LAM-US-101 bioavailability study.

Reviewer Note:
The Applicant's response is satisfactory. The dissolution profiles of 21 month exhibit batches were provided (\\cdsesub1\evsprod\nda212895\0016\m1\us\111-information-amendment\response-with-dissolution-profile-data.pdf).

Om Anand

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Zhuojun Zhao

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MOHAN K SAPRU
12/09/2019 08:26:23 AM