CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214439Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Divisional Memorandum

NDA: 214439 (NORLIQVA, amlodipine oral suspension)

Sponsor: CMP Development

Reviewer: N. Stockbridge, M.D., Ph.D.

The product is amlodipine oral suspension 1 mg/mL. The application received a Complete Response on 22 April 2021 for issues relating to two manufacturing sites. Other aspects of the application were acceptable; see CDTL memo dated 16 April 2021. The resubmission of 25 August 2021 and amended 6 January 2022 was reviewed by OPQ (Zhang, Khairuzzaman, Sahu, Adeeku, Adams, and Carver; 14 February 2022) with all issues resolved. One of the two manufacturing sites was replaced and the other was reinspected and found acceptable.

The review team and I concur on approval.

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/s/

NORMAN L STOCKBRIDGE
02/23/2022 07:32:43 AM

Cross-Discipline Team Leader Review

Date	April 16, 2021
From	Snehal Samant
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 214439
Type	505(b)(2)
Applicant	CMP Development LLC.
Date of Submission	June 22, 2020
PDUFA Goal Date	April 22, 2021
Proprietary Name / Established (USAN) names	NORLIQVA/ amlodipine
Dosage forms / Strengths	Oral solution / 1 mg/mL
Proposed Indications	Hypertension - Treatment of hypertension in adults and children 6 years and older, to lower blood pressure; Coronary artery disease - Chronic stable angina - Vasospastic angina (Prinzmetal's or Variant angina) - Angiographically documented coronary artery disease in patients without heart failure or an ejection fraction < 40%
OND Division	Division of Cardiology and Nephrology
Recommendation:	*'Complete Response'*

Material Reviewed/ Consulted	
Integrated Quality Review (03/26/2021)	Ben Zhang, Su (Suong) Tran (Drug substance), Akm Khairuzzaman, David Claffey (Drug product), Upasana Sahu, Rose Xu (Process and Facility), Eric Adeeku, Jesse Wells (Microbiology), Mohan Sapru (Application Technical Lead)
Pharmacology-Toxicology Review	N/A
Clinical Pharmacology Review (03/19/2021)	Kunal Jhunjhunwala, Snehal Samant
Clinical Review	N/A
Division of Medication Error Prevention and Analysis reviews (02/24/2021, 10/13/2020)	Mariette Aidoo, Hina S Mehta (02/24/2021) Carlos M Mena-Grillasca, Hina S Mehta, Chi-Ming Tu (10/13/2021)
Office of Study Integrity and Surveillance (03/31/3021)	Nicola M Fenty-Stewart
Office of Prescription Drug Promotion Review and Division of Medical Policy Programs	Jessica M Chung, Zarna Patel, Sharon R Mills, Lashawn M Griffiths

(03/24/2021)	

1. Introduction

On June 22, 2020, CMP Development LLC. submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for NORLIQVA (the final agreed upon proprietary name), amlodipine oral solution 1 mg/mL, for the following proposed indications:

- Treatment of hypertension in adults and in children 6 years and older, to reduce blood pressure
- Treatment of coronary artery disease (CAD): chronic stable angina, vasospastic angina (Prinzmetal's or variant angina), and angiographically-documented CAD in patients without heart failure or an ejection fraction of < 40%.

The application relies on the Agency's previous finding of safety and effectiveness for the listed drug, NORVASC® tablet (NDA 19787, approved 1992). No new clinical efficacy data are submitted in this application and no new claims are being sought with this application.

2. Background

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It is a peripheral-arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral-vascular resistance and reduction in blood pressure. In adults the recommended starting dose for patients with hypertension is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily dose. Amlodipine (2.5 to 5 mg once daily) is effective in lowering blood pressure in pediatric patients 6 to 17 years. The effect of amlodipine on blood pressure in patients < 6 years of age is not known. The recommended dose range for patients with coronary artery disease is 5 to 10 mg once daily.

The applicant proposes the same dose and dosing regimen for the oral solution of amlodipine as approved for NORVASC for the proposed indications.

3. Product Quality

Office of Pharmaceutical Quality (OPQ) does not recommend approval of the application due to deficiencies identified in the drug substance manufacturing and testing facilities.

Based on the integrated quality review by OPQ, manufacturing facilities-related deficiencies remain currently unresolved because of a) an official action indicated (OAI) classification for the drug substance testing facility, (b) (4) and b) a 704(a)(4) review of (b) (4) has identified currently unresolved CGMP deficiencies, resulting in 'withhold' recommendation for the facility. OPQ does not

recommend approval of the application in its present form until the above-mentioned deficiencies are satisfactorily resolved.

Drug substance

The drug substance Amlodipine Besylate, USP is a white crystalline powder. The drug substance, which has one chiral center (i.e., 2 enantiomers), is a racemic mixture, although only one isomer is a calcium channel blocker. The applicant has cross-referenced Type II DMF (b) (4), which along with DMF amendments have been previously reviewed and found to be adequate. Quality attributes of the drug substance such as polymorphism and particle size distribution are not critical for the oral solution dosage form and do not require controls. As per the OPQ review, the drug substance release specification includes testing the critical quality attributes (CQAs) and conforms to USP monograph. The retest period is (b) (4) months when stored according to the manufacturer's stated storage conditions.

Drug product

The proposed drug product is an oral solution containing 1 mg/mL amlodipine (equivalent to 1.385 mg of amlodipine besylate). The drug product contains the drug substance and inactive ingredients namely; Maltitol, Butylated Hydroxyanisole, Ethanol (b) (4), Glycerin, and (b) (4) Peppermint Flavor (b) (4). All excipient/inactive ingredients are USP/NF compendial designated and are controlled through their monograph-recommended specification. The maximum daily dose is 10 mg, which is equivalent to 10 mL of Amlodipine oral solution. The quantities of excipients used in the test formulation have been justified either because these are present in the formulation below the IIG limits, or do not exceed the acceptable limits for FDA-approved drug products for oral route, or a relevant safety assessment has been provided. OPQ review notes that the pharmaceutical development studies adequately support the formulation design, including excipient selection and excipient levels.

The proposed product Amlodipine oral solution 1 mg/mL is packaged in 150-mL Amber (b) (4) (b) (4) glass bottles with (b) (4) child-resistant closures. The proposed container closure system is appropriate for the intended use. The level of ethanol used in the formulation is reasonable for pediatric patient 6 years and older based on other FDA-approved products and FDA's inactive ingredient database.

OPQ review notes that the product release specification, involving testing of all the product CQAs, is adequate to ensure the consistent product quality. The non-compendial analytical procedures used for testing the drug product have been validated according to ICH guidelines. 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. OPQ review concludes that the product design, selection of excipients and control of product quality via release testing are adequate.

Manufacturing

As per the OPQ review, adequate information has been provided about incoming materials, and unit operations. The in-process controls, including the revised in-process control (b) (4) are adequate. Overall, the manufacturing process is well-controlled.

Microbiological aspects
In the proposed drug product, (b) (4) OPQ review notes that adequate antimicrobial validation data, per USP <51>, have been provided to support the minimum release and stability specification for the (b) (4) The product release specification includes microbial testing per USP <61> and USP <62>. The container closure system is designed to maintain the microbiological quality of the product.

Biopharmaceutics
As the drug product is an oral solution, a biopharmaceutics review is not applicable for this application.

Expiration date, stability and storage conditions
Based on the OPQ's assessment the stability data supports an expiration period of 24 months for the proposed product when stored at 20°C to 25°C (68°F to 77°F) in the commercial packaging. Excursions can be permitted to 15°C to 30°C (59°F to 86°F).

Facilities review/inspection
OPQ review notes that the drug product manufacturing facility, (b) (4) (b) (4) is deemed high risk because the facility has never been inspected before by FDA. A 704(a)(4) records review was conducted for this facility for an earlier non-sterile oral solution application, where the drug product was manufactured (b) (4) in the same facility. The 704(a)(4) review identified CGMP deficiencies, including deficient records of process parameters and in-process controls for certain unit operations. The firm's responses to 704(a)(4) deficiencies have been reviewed, but critical outstanding concerns remain unresolved. OPQ review concludes that the identified deficiencies are currently unresolved, resulting in 'withhold' recommendation for (b) (4) (b) (4)). The drug substance testing facility, (b) (4) is currently under the OAI. As a result, the facility remains out of compliance, and outstanding CGMP concerns preclude recommending the facility to be acceptable to support the drug substance testing role for this NDA.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted as part of the application. All nonclinical findings with NORVASC can be borrowed as the applicant has established an adequate bridge to the listed drug.

5. Clinical Pharmacology

Office of Clinical Pharmacology (OCP) recommends approval of amlodipine oral solution 1 mg/mL, pending the findings from bioanalytical site inspection. The applicant conducted an open-label, randomized, single-dose, 2-way crossover study (19-029) in healthy adults to evaluate the relative bioavailability (BA) of amlodipine oral solution 1 mg/mL (10 mL equivalent to the dose of 10 mg amlodipine) compared to the listed drug NORVASC tablet, 10 mg, following fasted state administration. The results show that both the peak concentration

(Cmax) and the area under the plasma concentration curve (AUC) of amlodipine oral solution are bioequivalent to NORVASC, thus establishing a bridge to borrow Agency's previous finding of safety and effectiveness for the listed drug NORVASC tablet.

The applicant conducted an open-label, randomized, single-dose, 2-way crossover food effect study (19-086) for amlodipine oral solution 1 mg/mL (10 mL equivalent to the dose of 10 mg amlodipine) in healthy adults. There was no effect of food on the pharmacokinetics of amlodipine following administration of the oral solution with a high fat, high calorie meal. The lack of food effect for the oral solution is consistent with the food effect results reported for NORVASC. The results of the relative BA study and food effect study support approval of amlodipine oral solution 1 mg/mL, to be taken with or without food, for the proposed indications at the doses as approved for the listed drug NORVASC tablet.

Site inspection
OCP requested inspection of the clinical and the bioanalytical sites of (b) (4) for the relative BA study 19-029. Office of Study Integrity and Surveillance (OSIS) determined that an inspection of the clinical site is not warranted at this time because the clinical site was inspected in February 2020, which falls within the surveillance interval. The final classification for the clinical site inspection was 'No Action Indicated' (NAI). Results from OSIS bioanalytical site inspection are pending at the time this review.

6. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, the relative bioavailability study (19-029) provides the bridge to the efficacy findings of the listed drug, NORVASC, for treatment of hypertension, and coronary artery disease.

7. Safety

This application primarily relies on the Agency's previous determination of safety for the listed drug, NORVASC.

8. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held or needed.

9. Pediatrics

The product triggers Pediatric Research Equity Act (PREA) because the drug product is a new dosage form. The applicant requested full waiver for the entire pediatric population with coronary artery disease on the basis that studies are impossible or highly impracticable as this disease occurs rarely in children.

Given that NORVASC is approved for the treatment of hypertension in pediatric patients 6 to < 17 years of age, studies are not needed to establish safety and effectiveness in this population. The applicant requested deferral for pediatric patients with hypertension from birth to < 6 years of age. PeRC agreed with granting the full waiver and deferral as requested.

(b) (4)

10. Other Relevant Regulatory Issues

None.

11. Labeling

A final agreement on labeling was not reached with the applicant because of the planned 'Complete Response' action at the end of the review cycle.

Proprietary name

The originally proprietary name (b) (4) was denied by DMEPA because the name may be confused with applicant's pending proposed proprietary name for another drug product, due to similarity in spelling, orthographic and phonetic similarities, and overlapping product characteristics. The revised proprietary name, NORLIQVA, is accepted by DMEPA.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

'Complete Response' – Because of official action indicated (OAI) classification for the drug substance testing facility, (b) (4) and currently unresolved CGMP deficiencies, resulting in 'withhold' recommendation for (b) (4)

Risk Benefit Assessment

For the indications sought, the risk-benefit of NORLIQVA when used as directed in the proposed label is not expected to be different compared to NORVASC.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

Recommendation for other Postmarketing Requirements and Commitments
None

Recommended Comments to Applicant
Additional comments related to drug product manufacturing to be outlined in the Complete Response letter.

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/

SNEHAL N SAMANT
04/16/2021 01:11:32 PM

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