CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212895Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	December 13, 2019
From	Sudharshan Hariharan
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 212895
Type	505(b)(2)
Applicant	CSPC Ouyi Pharmaceutical Company
Date of Submission	February 28, 2019
PDUFA Goal Date	December 28, 2019
Proprietary Name / Established (USAN) names	CONJUPRI / Levamlodipine maleate
Dosage forms / Strengths	Tablet / 1.25, 2.5 and 5 mg
Approvable Indication(s)	Treatment of hypertension in adults and children 6 years and older
OND Division	Division of Cardiovascular and Renal Products
OND Division Director	Norman Stockbridge
Recommendation:	*'Approval'*

Material Reviewed/Consulted	
Integrated Quality Review (12/09/19)	Kabir Shahjahan, Suong Tran (Drug Substance), Mariappan Chelliah, Wendy Wilson-Lee (Drug Product), Ruth Moore, Zhong Li (Process and Facility), Om Anand, Zhuojun Zhao (Biopharmaceutics), Mohan Sapru (Application Technical Lead)
Pharmacology-Toxicology Review (07/09/19)	Philip Gatti, Xuan Chi
Clinical Pharmacology Review (12/02/19)	VenkateswaranChithambaramPillai, Sudharshan Hariharan
Clinical Review (11/05/19)	Maryann Gordon, Karen Hicks
Division of Medication Error Prevention and Analysis Reviews (07/16/19, 09/13/19, 11/04/19)	Sarah Thomas, Chi-Ming Tu, Danielle Harris
Office of Study Integrity and Surveillance (05/14/19, 09/06/19)	Li-Hong Yeh, Xiaohan Cai, Ruben Ayala, Arindam Dasgupta, Himanshu Gupta, Stanley Au, Seongeun Cho
Office of Prescription Drug Promotion Review (11/01/19)	Zarna Patel
Division of Medical Policy Programs - Patient Labeling Review (11/08/19)	Morgan Walker, Zarna Patel, Lashawn Griffiths

1. Introduction

Amlodipine besylate (NORVASC) is approved by the FDA for the treatment of hypertension and coronary artery disease (CAD). Amlodipine is a 1:1 racemic mixture of (S)-amlodipine (the levorotatory L-form) and (R)-amlodipine (the dextrorotatory D-form). CSPC Ouyi Pharmaceutical Company submitted this NDA to seek marketing approval for the use of levamlodipine maleate tablet (Tradename: CONJUPRI) for the treatment of hypertension under the 505(b)(2) regulatory pathway. Levamlodpine is approved and marketed in China since 2003.

The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, NORVASC tablets (NDA 19787, approved 1992). No new clinical efficacy studies were conducted to support this application and no new claims are being sought.

2. Background

Amlodipine is a dihydropyridine calcium antagonist 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. However, amlodipine exists as a 1:1 mixture of two enantiomers. Literature reports indicate that the (S)-enantiomer has L-type channel blocking activity while the R-enantiomer has about 1,000-fold weaker activity. Further, (S)-amlodipine is not converted to (R)-amlodipine in vivo.

In adults the recommended starting dose of amlodipine is 5 mg/day with a maximum dose of 10 mg/day. Amlodipine (2.5 to 5 mg daily) is effective in lowering blood pressure in pediatric patients 6 to 17 years. The recommended dose of levamlodipine for the treatment of hypertension is half as that approved for NORVASC.

The proposed dosage strengths to-be-marketed in the US are 1.25, 2.5 and 5 mg levamlodipine tablets (b) (4) The applicant proposes the same dosing regimen of once-daily as NORVASC. (b) (4) the applicant seeks a marketing claim only for the hypertension indication for levamlodipine tablets in this NDA.

3. Product Quality

Office of Product Quality (OPQ) recommends approval of the application from a quality perspective. The review notes that the non-proprietary name approved by the USAN Council is 'levamlodpine'. Hence the name 'levamlodpine' and not (b) (4) is used throughout this review.

Drug substance

The applicant has cross-referenced DMF (b) (4) for the manufacturing of amlodipine base (b) (4) The optical purity of the drug substance is controlled (b) (4) The (b) (4) impurity of the drug substance is monitored (b) (4) with a limit of ≤ (b) (4)%. The batch analysis data of 3 commercial drug substance batches conform to the proposed specification. Based on stability data, the drug substance has a retest period of (b) (4) months. As per OPQ review, the information regarding the structural characterization, manufacturing process and release specification is acceptable.

Drug product

The applicant intends to market 3 different strengths of levamlodipine tablet: 1.25, 2.5 and 5 mg. There is a score on 2.5 and 5 mg strengths (b) (4)

As per the OPQ review, the product release specification, involving testing of all the product critical quality attributes (CQAs), is adequate to assure the identity, strength, quality, purity, potency and batch-to-batch consistency through the product's lifecycle. The batch data demonstrate that the applicant can manufacture the tablets with a consistent quality that meets the specification. (b) (4)

The manufacturing process involves (b) (4)

Biopharmaceutics

As per the OPQ review, the proposed dissolution method is acceptable for the QC of the proposed drug product. It also agrees with granting biowaiver to the 1.25 mg strength of levamlodipine tablet based on dissolution and other supportive data.

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). As per OPQ review, the components of the proposed container closure system meet appropriate regulations and are suitable for packaging the drug product.

Expiration Date and Storage Conditions

Based on the OPQ's assessment of stability data, the proposed product shelf-life of 24 months, when stored at controlled room temperature of 20 to 25°C (68 to 77°F), is acceptable.

Facilities review/inspection
All currently listed manufacturing facilities are deemed acceptable by Office of Process and Facilities.

4. Nonclinical Pharmacology/Toxicology

The nonclinical studies submitted and accepted by the Division as adequate for approval include:

- efficacy or pharmacodynamic studies in normotensive as well as hypertensive animal models
- published data that proves that the (R)- or dextroamlodipine has no significant calcium channel blocking activity and thus antihypertensive effect
- a 6-week repeat-dose general toxicology study in beagle dogs with a 28-day recovery period.

For data pertaining to genetic toxicology, reproductive toxicology and carcinogenicity, the applicant, via the 505(b)(2) pathway, is relying on the Agency's findings from nonclinical studies conducted for NORVASC. The reliance on NORVASC is acceptable as the applicant has established an adequate bridge to the listed drug.

The nonclinical review asserts that in vitro studies submitted by the applicant demonstrate that (S)-enantiomer blocks the calcium channel, while (R)-amlodipine does not show any pharmacological activity at the calcium channel. Further, in vivo nonclinical studies demonstrate that (S)-enantiomer at half doses produces similar reductions in blood pressure (albeit with modest variability which is expected across different studies/animal models) compared to racemic amlodipine at full doses, corroborating that (R)-amlodipine does not have any antihypertensive effect. The 6-week repeat-dose general toxicology study did not identify any new safety issue that were already identified with the racemate.

5. Clinical Pharmacology

Office of Clinical Pharmacology (OCP) recommends approval of levamlodipine maleate tablets for the treatment of hypertension. The applicant conducted a randomized, three-way crossover study (Study LAM-US-101) characterizing the pharmacokinetics of (S)-amlodipine following administration of 5 mg levamlodipine maleate tablet and 10 mg of the listed drug, NORVASC, under fasted conditions. The study also assessed the effect of food on 5 mg levamlodipine maleate tablet. The results show that both the peak concentration (C_{max}) and the area under the curve (AUC) for (S)-amlodipine is bioequivalent between 5 mg levamlodipine maleate tablet and 10 mg NORVASC, thus establishing a bridge to borrow Agency's previous finding of safety and effectiveness for NORVASC pertaining to the hypertension indication. There was no effect of food on the pharmacokinetics of (S)-amlodipine following administration of 5 mg levamlodipine maleate tablet with a high fat meal. The lack of food effect for levamlodipine maleate tablet is consistent with the food effect results reported earlier for NORVASC. The applicant also conducted a pilot two-way crossover relative bioavailability study (Study 73912) that compared the exposures of (S)-amlodipine between 2.5 mg levamlodipine maleate tablet and 5 mg NORVASC. The results of the pilot study also showed bioequivalence for C_{max} and AUC of (S)-amlodipine between the two tested formulations. The applicant sought a biowaiver for the lowest strength of 1.25 mg.

Site Inspection
OCP requested inspection of the clinical (Collaborative Neuroscience Network LLC, Long Beach, CA) and bioanalytical site (b) (4) for Study LAM-US-101. OSIS recommends accepting data from these studies.

6. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, the relative bioavailability study provides the bridge to the efficacy findings of the listed drug, NORVASC, pertaining to the hypertension indication. Because the potency pertaining to the antihypertensive effect was demonstrated to reside primarily in the (S)-enantiomer of amlodipine, the applicant was not required to conduct any clinical efficacy studies. Nonetheless, the applicant submitted legacy efficacy and safety data obtained from post-approval studies conducted by the applicant in China as supportive evidence. In the absence of patient level data from these studies and the lack of a prospective statistical analysis plan, only a cursory review of the topline results of these studies was conducted. The review generally identified that levamlodipine maleate tablet at 2.5 mg produced similar antihypertensive effect compared to NORVASC at 5 mg in hypertensive patients.

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

This application triggers Pediatric Research Equity Act (PREA) because it contains a new active ingredient. 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 a deferral of pediatric studies in patients from birth to less than 6 years of age with hypertension in the agreed initial pediatric study plan. The PeRC agreed to the request for deferral.

The Division recommends the following studies as post-marketing requirements (PMR):

- Conduct nonclinical toxicity study in juvenile rats (b) (4)

- Conduct a pharmacokinetic, pharmacodynamic, and safety study in patients with hypertension <6 years of age

Because calcium ions and L-type voltage dependent calcium channels are involved in multiple physiological processes from embryonic development through adulthood, including those in neurosecretion, hypothalamic rhythm generation, and reproductive development, the Division requests a juvenile toxicity study applicable to humans ages <6 years to assess for effects on reproductive and learning development prior to conducting a clinical study in patients <6 years of age.

10. Other Relevant Regulatory Issues

None.

11. Labeling

There are no unresolved labeling issues. An agreement with the applicant has been reached on the proposed alterations to the label.

Proprietary name: The proposed proprietary name, CONJUPRI, is accepted by DMEPA.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval

Risk Benefit Assessment
For the indications sought, the risk-benefit of CONJUPRI 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 (PMR) and Commitments (PMC)

The following items are PMRs:

- Conduct nonclinical toxicity study in juvenile rats (b) (4)

- Conduct a pharmacokinetic, pharmacodynamic, and safety study in patients with hypertension <6 years of age

(b) (4)

Recommended Comments to Applicant
None

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/

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