Cross-Discipline Team Leader Review

Date	August 14, 2024
From	Brianna Cote
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 218772
Type	505(b)(2)
Applicant	Scienture Inc
Date of Submission	10/19/23
PDUFA Goal Date	8/19/23
Proprietary Name	ARBLI
Established or Proper Name	Losartan potassium
Dosage Form(s)/Strengths	Oral suspension/10 mg/mL
Proposed Indication(s)	• Treatment of hypertension, to lower blood pressure in adults and children greater than 6 years old. • Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy. • Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension.
Recommendation on Regulatory Action	**Complete Response**

Material Reviewed/Consulted	
Integrated Quality Review (8/8/24)	Ben Zhang, Zhengfu Wang (Drug Substance), Ali Mohamadi, Theodore Carver (Drug Product/Labeling), Upasana Sahu, Sateesh Kumar (Manufacturing), Jianli Xue, Nandini Bhattacharya (Microbiology), Theodore Carver (Application Technical Lead)
Pharmacology-Toxicology Review (6/11/24)	Narendranath R Chintagari, Sree Rayavarapu
Clinical Pharmacology Review (7/8/24)	Po-Hung Hsieh, Brianna Cote
Clinical Review (3/11/24)	Maryann Gordon, Fortunato F Senatore
Division of Pediatric and Maternal Health Review (7/24/24)	Jane E Liedtka, Tamara N Johnson, Lynne P Yao
Division of Medication Error Prevention and Analysis Reviews (1/18/24, 7/8/24, 7/29/24)	Tayler E Nalesnik (1/18/24), Hina S Mehta (1/18/24), Jody K Kundreskas (7/8/24, 7/29/24), Nicole F Iverson (1/18/24, 7/8/24, 7/29/24)
Office of Study Integrity and Surveillance Reviews (12/14/23, 5/30/24)	James J. Lumalcuri (12/14/23), Makini Cobourne-Duval (5/30/24), Mei Ou (5/30/24), Seongeun Cho (5/30/24)
Office of Prescription Drug Promotion Review (7/2/24)	Meena R Savani

1. Introduction

On October 19, 2023, Scienture Inc submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ARBLI (the final agreed upon tradename), an oral suspension of losartan potassium, for the treatment of the following indications:

- Treatment of hypertension, to lower blood pressure in adults and children greater than 6 years old. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
- Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy. There is evidence that this benefit does not apply to Black patients.
- Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension.

The application relies on the Agency's previous findings of the safety and effectiveness of the reference listed drug, COZAAR (NDA 020386, approved April 14, 1995). No new clinical efficacy data are submitted in this application, and no new claims are being sought with this application.

2. Background

Angiotensin II, formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme, is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system, and an important component in the pathophysiology of hypertension. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite, losartan carboxylic acid, block angiotensin II and its aldosterone-secreting effects by blocking the binding of angiotensin II to the angiotensin II type 1 (AT1) receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, noncompetitive inhibitor of the AT1 receptor.

In adults, the usual adult dose for hypertension is 50 mg once daily. The usual starting dose is 50 mg once daily for hypertensive patients with left ventricular hypertrophy, and hydrochlorothiazide can be added or the losartan dose can be increased to 100 mg if further blood pressure response is needed. The usual dose is 50 mg once daily for nephropathy in type 2 diabetic patients, but the dose can be increased to 100 mg once daily if further blood pressure response is needed. The usual pediatric starting dose for hypertension is 0.7 mg/kg once daily (up to 50 mg), and doses can be adjusted according to blood pressure response, though doses above 1.4 mg per kg (or in excess of 100 mg) daily have not been studied. The Applicant has developed a losartan oral suspension which can provide an alternative to compounding of losartan tablets into a suspension. The Applicant proposes the same dose and dosing regimen for the oral suspension of losartan as approved for COZAAR.

3. Product Quality

The Integrated Quality Review from the Office of Pharmaceutical Quality (OPQ) does not recommend approval of the application due to deficiencies identified in the drug product review.

Drug Substance (Losartan Potassium)
Losartan Potassium is a [redacted] small molecule with no chiral centers. It was determined that the specifications for the drug substance included in the NDA are adequate to support the quality of the drug substance.

Drug Product (Losartan Potassium Oral Suspension)
The drug product is a white, translucent suspension with a peppermint odor. [redacted]

The Applicant included particle size distribution (PSD) and dissolution, and the final drug product specification includes tests for appearance, identity, specific gravity, weight loss, viscosity, deliverable volume, [redacted], pH, particle size, homogeneity, losartan potassium assay, [redacted] content, dissolved fraction, degradants, microbial limits, specified organisms, and antimicrobial effectiveness. The Applicant also developed a method upon FDA request to measure the fraction of dissolved drug substance.

FDA identified concerns related to the stability data provided, including the PSD test and assays for losartan [redacted] assay variability issues and invalidated out-of-trend (OOT) and out-of-specification (OOS) results were observed during stability studies for stability drug product batches and one of the process performance qualification batches. Low assay values and invalidated OOS results were not adequately investigated in reports and other information provided in response to information requests. [redacted] Due to these deficiencies, the drug product information is inadequate to support the quality of the drug product for the duration of its shelf life, and the stability data are inadequate to support assignment of a shelf life to the drug product.

Manufacturing
After the Applicant addressed information requests related to process parameters and controls, the manufacturing process and controls were found to be adequate to support the quality of the drug product. Additionally, the manufacturing facilities were all recommended for approval based on previous inspection history.

Biopharmaceutics
Losartan was determined to be fully dissolved in the drug product, so no dissolution testing was required. Scientific bridging between the proposed and listed drug products was established with

a comparative bioavailability study. Therefore, no biopharmaceutics review as required for this NDA.

Microbiology
After the Applicant addressed information requests related to supporting studies, it was determined that the tests, studies, and other information provided in the NDA are adequate to support the microbiological quality of the drug product.

Quality Labeling
Final review of the quality aspects of the product labeling will be completed after the deficiencies have been addressed and the NDA is resubmitted for review.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology review team recommends approval. No new nonclinical studies were submitted as part of the application, and the Applicant proposed to rely on the FDA's findings of safety and efficacy as in the listed drug (LD) labeling and establish a scientific bridge to the LD via a clinical bioequivalence study in healthy adult volunteers.

The Nonclinical Pharmacology/Toxicology reviewer found that the excipients used in the proposed drug product composition have maximum daily intake levels (MDI) at the maximum daily dose of the drug product that are similar to or lower than their MDI levels in the other approved drug products.

The safety qualification of two impurities were assessed:

- Losartan related compound D (also known as 1H-Dimer)
    - Chemical name: 5-[4'-({2-butyl-5-[(5-{4' -[(2-butyl-4-chloro-5-hydroxy methyl-1H-imidazol-1-yl) methyl] biphenyl-2-yl} -1H tetrazol-1-yl) methyl]-4-chloro-1H-imidazol-1-yl}methyl) biphenyl-2-yl] tetrazol, potassium salt
- Losartan related compound E (also known as 2H-Dimer)
    - Chemical name: 5-[4'-({2-Butyl-5-[(5-{4'-[(2-butyl-4-chloro-5-hydroxymethyl-1H-imidazol -1-yl)methyl] biphenyl-2-yl}-2H tetrazol-2-yl)methyl]-4-chloro-1H-imidazol-1-yl}methyl)biphenyl-2-yl] tetrazol, potassium salt

The Applicant proposed to control these two impurities at not-more-than (NMT) 0.5% each, with the MDI of losartan-related compounds D & E at the proposed specification limit being 0.5 mg/day. Quantitative structure activity relationship analysis predicted that the impurities are negative for bacterial mutagenicity potential. The Applicant-proposed specification limit of NMT 0.5 mg/day for each of the impurities is higher than the ICH Q3B qualification limit of NMT 0.2 mg/day. The Nonclinical Pharmacology/Toxicology reviewer notes that the Applicant-proposed specification limit for each of these two impurities are compliant with the USP monograph for the losartan oral tablet, and it was concluded that the Applicant-proposed NMT

0.5% specification to control each of the impurities in the proposed drug product does not raise safety concerns.[1]

5. Clinical Pharmacology

Office of Clinical Pharmacology (OCP) recommends approval of the oral suspension of losartan with or without food. The Applicant conducted two studies as follows:

1. A relative bioavailability study (Study 14323/21-22) to assess the relative bioavailability of a single oral dose of the losartan potassium oral suspension compared with COZAAR under the fasting condition
2. A food effect study (Study 14324/21-22) to assess the effect of food on the rate and extent of absorption of losartan and its major metabolite, losartan carboxylic acid, after a single oral dose of the losartan potassium oral suspension administered immediately after a meal (fed condition) as compared to administration under the fasting condition

The results of the relative bioavailability study (Study 14323/21-22) demonstrated that a 100 mg dose of the losartan potassium oral suspension under fasting conditions had a similar AUC compared with COZAAR 100 mg tablets administered under fasting conditions. However, the geometric mean ratio Cmax for losartan in the losartan suspension was approximately 35% higher than COZAAR (90% CI of ratio 122%, 150%). This approximately 35% higher Cmax does not appear to be clinically relevant, as one published study showed were no dose-related trends for adverse events for losartan doses up to 150 mg, and there appeared to be a flat dose-response for changes in supine diastolic blood pressure (SuDBP) for losartan doses above approximately 50 mg.[2] Considering the flat dose-response relationship, the AUC data, and that higher doses do not seem to increase the risk of adverse events, the PK differences noted do not appear to be of concern.

The results of the food effect study (Study 14324/21-22) demonstrated that taking losartan potassium oral suspension with a high-fat, high-calorie meal slowed the absorption of losartan and decreased its Cmax (losartan fed versus fasted Cmax geometric mean ratio 24.6%, 90% CI of ratio 21.5%, 28.0%; losartan carboxylic acid fed versus fasted Cmax geometric mean ratio 47.7%, 90% CI of ratio 43.2%, 52.6%). Administration with food had minor effects on the AUC of losartan and losartan carboxylic acid, with the lower bound of the losartan carboxylic acid narrowly missing the 80 to 125% range (78.7% and 78.9% for AUC_{0-t} and $AUC_{0-\infty}$, respectively). In Section 12.3 of the COZAAR label, it is noted that "A meal slows absorption of losartan and decreases its Cmax but has only minor effects on losartan AUC or on the AUC of the metabolite (~10% decrease)." Therefore, there appears to be a food effect on the Cmax of the reference product, though the magnitude was not specified; however, no dose adjustment or food restriction is required per COZAAR labeling, suggesting that a decrease in Cmax is not a concern. Additionally, the COZAAR labeling text in Section 12 states: "Mean peak

[1] USP monograph; Losartan potassium tablets; https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/losartan_potassium_tablets.pdf(Accessed on 06/10/2024)

[2] Gradman AH, Arcuri KE, Goldberg AI, Ikeda LS, Nelson EB, Snavely DB, Sweet CS. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. Hypertension. 1995 Jun;25(6):1345-50. doi: 10.1161/01.hyp.25.6.1345. PMID: 7768585.

concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours"; on the other hand, "a dose of 100 mg inhibits the pressor effect by about 85% at peak (6 hours after dosing) with 25-40% inhibition persisting for 24 hours." It appears the effect of losartan is not mainly driven by Cmax, as plasma concentrations decrease within a few hours, and the persisting effect is more likely driven by AUC. Further, as described in a published study, there appears to be only a slight reduction in blood pressure lowering effect between peak effect and trough effect measured at 6 hours post dose and 24 hours post dose, respectively, while there is a significant drop in drug concentration between Cmax and Ctrough, which also indicates that AUC is more important than Cmax for efficacy.[3] Therefore, as the effect of losartan appears to be driven more by AUC rather than Cmax, dosing under either fed or fasted conditions appears reasonable for the losartan potassium oral suspension formulation.

Site Inspection:

OCP requested inspection of the clinical and bioanalytical sites at (b) (4) The Office of Study Integrity and Surveillance (OSIS) declined to conduct an on-site inspection of the clinical site, as the Office of Regulatory Affairs conducted an inspection of the site in (b) (4) for the submission of a different product. OSIS conducted a remote regulatory assessment of the analytical site of Study 14323/21-22, no objectional conditions were observed, and there were no identified concerns for the reliability of the data for the inspected study.

6. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, the relative bioavailability study provides the bridge to the efficacy findings of the listed drug, COZAAR.

7. Safety

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

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 is a new dosage form of losartan. The Applicant submitted their agreed-upon Initial Pediatric Study Plan (iPSP) with the application. The Agreed iPSP contained a plan for (b) (4) a partial waiver in patients 0 to < 2 years of age for the treatment of hypertension (b) (4)

[3] Gradman AH, Arcuri KE, Goldberg AI, Ikeda LS, Nelson EB, Snavely DB, Sweet CS. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. Hypertension. 1995 Jun;25(6):1345-50. doi: 10.1161/01.hyp.25.6.1345. PMID: 7768585.

[redacted] (b) (4) and a plan to conduct a deferred safety and pharmacokinetic study in patients 2 to < 6 years of age with hypertension.

The Agreed iPSP also contained a plan for a full waiver for the entire pediatric age range for the reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy, and for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension, because these conditions rarely occur in pediatric patients; hence, studies would be impossible or highly impractical.

The Division and Pediatric Review Committee (PeRC) agreed with the proposed full waivers, partial waiver, and deferred study as detailed above. If/when approved, the Pediatric Use subsection of the label should describe the safety concern in children less than 2 years of age, and this information should be summarized in other sections of the label as appropriate. If/when approved, a post-marketing requirement (PMR) should be issued for a safety and pharmacokinetic study to identify a dosing regimen for losartan potassium in pediatric patients 2 to less than 6 years of age with hypertension.

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. The proposed proprietary name, ARBLI, was found conditionally acceptable in the current review cycle.

[redacted] (b) (4)

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12. Recommended Regulatory Action

The recommended regulatory action is a Complete Response because of deficiencies identified in the drug product review related to the analytical procedure for particle size, changes in the drug product observed during stability studies that are not adequately described or characterized in the NDA, and the investigations of OOS and OOT results for the losartan assay and other tests as well the apparent inhomogeneity of the drug product were incomplete with respect to determining root causes and corrective actions.

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