CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218772Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION MEMORANDUM

Application number:	NDA 218772
Supporting document/s:	24
Applicant's letter date:	09/17/2024
CDER stamp date:	09/17/2024
Product:	Arbli® (Losartan oral suspension; 10 mg/mL)
Indication:	(b) (4)
Applicant:	Scienture Inc.
Review Division:	Division of Pharm/Tox for Cardiology, Hematology, Endocrinology, and Nephrology (DPT-CHEN)
Reviewer:	Narendranath Reddy Chintagari, BVSc & AH (DVM); MVSc, PhD
Team Leader:	Sree Rayavarapu, DVM, PhD
DPT-CHEN Director:	Todd Bourcier, PhD
Project Manager:	Sabry Soukehal, RAC, DCPM

Template Version: September 1, 2010

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Except as specifically identified, all data and information discussed below and necessary for approval of NDA 218772 are owned by Scienture or data for which Scienture has obtained a written right of reference. Any information or data necessary for approval of NDA 218772 that Scienture does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 218772.

Memorandum

Scienture Inc. submitted NDA 218772 for marketing approval of Arbli®, an oral suspension formulation of losartan potassium (10 mg/mL) via 505(b)(2) pathway. The listed drug (LD) is Cozaar® (losartan potassium, tablets) under NDA 020386. The NDA 218772 applicant is seeking approval for the proposed losartan potassium, oral suspension for same indications, and dosing regimen as the LD. The maximum daily dose (MDD) in adults is 100 mg/day and in pediatric patients is 0.7 mg/kg/day (up to 50 mg/day).

No new nonclinical studies were conducted in support of the proposed losartan potassium oral suspension product. DCN-Pharm/Tox previously concluded that the losartan potassium oral suspension (10 mg/mL) is approvable from a nonclinical perspective.[1] A complete response was issued based on Quality deficiencies regarding drug product.[2]

The applicant responded to the complete response on 09/17/2024.[3] The applicant claimed that (b) (4)

Pharm/Tox re-evaluated the excipient levels used in the formulation and reiterated that all excipients in the proposed formulation are at levels in previously approved drugs of same route of administration. Pharm/Tox informed that if the bioequivalence and pharmacokinetic parameters of the proposed formulation are comparable with LD and are deemed acceptable from Quality and clinical pharmacology perspectives then there are no expected safety concerns from a Pharm/Tox perspective.

[1] NDA 218772; Losartan potassium; Rev-nonclinical-21 (Primary Review); Dated 06/11/2024
[2] NDA 218772; Losartan potassium; Cor-NDA Action; Dated 08/19/2024
[3] NDA 218772; Losartan potassium; EDR; SDN 24; Module 1.2. Cover Letters

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/s/

NARENDRANATH R CHINTAGARI
02/05/2025 04:54:55 PM

SREE RAYAVARAPU
02/05/2025 04:59:45 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION MEMORANDUM

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Applicant's letter date:	10/19/2023
CDER stamp date:	10/19/2023
Product:	Arbli® (Losartan oral suspension; 10 mg/mL)
Indication:	(b) (4)
Applicant:	Scienture Inc.
Review Division:	Division of Pharm/Tox for Cardiology, Hematology, Endocrinology, and Nephrology (DPT-CHEN)
Reviewer:	Narendranath Reddy Chintagari, BVSc & AH (DVM); MVSc, PhD
Team Leader:	Sree Rayavarapu, DVM, PhD
DPT-CHEN Director:	Todd Bourcier, PhD
Project Manager:	Silvia Bartlett, BS

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Nonclinical Review

Scienture Inc. submitted NDA 218772 for marketing of Arbli®, an oral suspension formulation of losartan potassium (10 mg/mL) via a 505(b)(2) pathway. The listed drug (LD) is Cozaar® (Losartan potassium, tablets) under NDA 020386. Cozaar® is an angiotensin II receptor blocker indicated for the treatment of i) hypertension in adults and children >6 years old ii) reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy and iii) treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension. The maximum daily dose (MDD) in adults is 100 mg/day and in pediatric patients is 0.7 mg/kg/day (up to 50 mg/day).

The NDA 218772 applicant is seeking approval for the proposed losartan potassium, oral suspension for same indication, and dosing regimen as the LD. For the approval of the drug product, the applicant proposed to rely on the FDA's findings of safety and efficacy as in the LD labeling and also establish a scientific bridge to the LD via a clinical bioequivalence study in healthy adult volunteers.

No new nonclinical studies were conducted in support of the proposed losartan potassium oral suspension product.

This reviewer looked at the excipients used in the proposed drug product composition and determined that their maximum daily intake levels (MDI) at the MDD of the drug product are comparable or lower than their MDI levels in the approved drug products of similar context of use.

The Quality team consulted (email communication dated 02/22/2024) nonclinical regarding the safety qualification of two impurities:

i) 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

ii) 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 the two impurities, losartan related compounds D & E in the drug product at not-more-than (NMT) 0.5% each. The MDI of losartan related compounds D & E at the proposed specification limit is 0.5 mg/day.

The applicant submitted ICH M7-compliant quantitative structure activity relationship [(Q)SAR] analysis to evaluate the bacterial mutagenicity potential of the impurities. The

applicant's (Q)SAR analysis predicted that the impurities D & E are negative for bacterial mutagenicity potential. This reviewer agrees with the applicant analysis. The applicant proposed specification limit NMT 0.5 mg/day for each of the impurities is higher than ICH Q3B qualification limit of NMT 0.2 mg/day.

The applicant qualified the general toxicity of each of the impurities using a read-across approach. The general toxicity evaluation of impurities using a read-across approach is not acceptable; however, the applicant proposed specification limit for each of the impurities losartan related compound D and E are compliant with USP monograph for losartan oral tablet.[1] The applicant proposed NMT 0.5% specification to control each each of the impurities D and E in the proposed drug product does not raise safety concerns from a nonclinical perspective.

This reviewer compared the proposed labeling to that of the listed drug. No changes were proposed to the nonclinical relevant sections (Sections 8, 12, and 13). There are no nonclinical comments for the proposed labeling.

The proposed 505(b)(2) losartan potassium oral suspension (10 mg/mL) is approvable from a nonclinical perspective.

[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)

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/s/

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06/11/2024 01:21:25 PM

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06/11/2024 01:47:10 PM