CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218772Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 4, 2025
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 218772
Product Name, Dosage Form, and Strength:	Arbli (losartan potassium) oral suspension, 10 mg/mL
Applicant Name:	Scienture LLC
FDA Received Date:	February 27, 2025
TTT ID #:	2023-6874-3
DMEPA 2 Safety Evaluator:	Julie Neshiewat, PharmD, MS, BCPS, CPH
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Scienture LLC submitted revised container label and carton labeling received on February 27, 2025 for Arbli. We reviewed the revised container label and carton labeling for Arbli (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] The revisions are also in response to recommendations from the Office of Pharmaceutical Quality (OPQ) to express the strength in a specific format with an equivalency statement and to alphabetically order the excipients.

2 CONCLUSION

Scienture LLC implemented all of our recommendations and clarified that they intend to use the expiration date format of "YYYY-MM-DD" (numerical characters to represent the month) for both the container label and carton labeling . We have no additional recommendations at this time.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

[a] Neshiewat, J. Label and Labeling Review for Arbli (NDA 218772). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 FEB 18. TTT ID: 2023-6874-2.

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/s/

JULIE V NESHIEWAT
03/04/2025 10:04:29 AM

NICOLE F IVERSON
03/04/2025 02:46:53 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 18, 2025
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 218772
Product Name, Dosage Form, and Strength:	Arbli (losartan potassium) oral suspension, 10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Scienture LLC
FDA Received Date:	September 17, 2024 and October 1, 2024
TTT ID #:	2023-6874-2
DMEPA 2 Safety Evaluator:	Julie Neshiewat, PharmD, MS, BCPS, CPH
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Arbli (losartan potassium) oral suspension, we reviewed the proposed Arbli Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Arbli (losartan potassium) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Cozaar (losartan potassium), NDA 020386.

1.2 REGULATORY HISTORY

Scienture LLC previously submitted NDA 218772 on October 19, 2023. We completed a label and labeling review at that time.[a] On July 12, 2024, our recommendations for the container label and carton labeling were sent to the Applicant and on July 24, 2024, the Applicant responded and provided a revised container label and carton labeling. We completed a label and labeling memo on July 29, 2024 and had no further recommendations at that time[b]. We note that all of our recommendations for the container label and carton labeling were implemented. On August 19, 2024, the application received a Complete Response (CR) letter due to issues with product quality. The CR letter stated that FDA reserved comments on the proposed labels and labeling until the application is otherwise adequate.[c]

Thus, Scienture LLC submitted a Class 2 Resubmission on September 17, 2024.[d] The Applicant submitted a labeling amendment on October 1, 2024 to update the Applicant's name from "Scienture Inc." to Scienture LLC" on the Prescribing Information, container label, and carton labeling.[e]

2 MATERIALS CONSIDERED

This section lists the materials considered for our review of NDA 218772.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A

[a] Kundreskas, J. Label and Labeling Review for Arbli (NDA 218722). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUL 08. TTT ID No.: 2023-6874.

[b] Kundreskas, J. Review of Revised Label and Labeling for Arbli (NDA 218722). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUL 29. TTT ID No.: 2023-6874-1.

[c] Bartlett, S on behalf of Norman Stockbridge. Complete Response for NDA 218772. Silver Spring (MD): FDA, CDER, OND, Division of Cardiology and Nephrology (DCN) (US); 2024 AUG 19.

[d] Resubmission/Complete Response Amendment (NDA 218772 and Arbli). Commack (NY): Scienture Inc; 2024 SEP 17. Available from: \\CDSESUB1\EVSPROD\nda218772\0024\m1\us\1-2-cover-letter-pdf.pdf.

[e] Labeling Amendment (NDA 218772 and Arbli). Commack (NY): Scienture LLC; 2024 OCT 01. Available from: \\CDSESUB1\EVSPROD\nda218772\0027\m1\us\1-2-cover-letter-pdf.pdf

Labels and Labeling	B
Previous DMEPA Reviews	C

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), container label, and carton labeling for Arbli to identify deficiencies that may lead to medication errors and other areas of improvement.

We note that the proposed Arbli oral suspension has the same active ingredient (losartan potassium), indications, recommended dosage, and route of administration (oral) as the Listed Drug (LD), Cozaar. However, there are differences between the proposed product and the LD in dosage form and packaging. The proposed product will be available in a 165 mL bottle of a 10 mg/mL oral suspension whereas the LD is approved as 25 mg, 50 mg, and 100 mg tablets. Additionally, we note that the LD labeling includes instructions for the preparation of a 200 mL bottle of a 2.5 mg/mL oral suspension utilizing ten 50 mg tablets which can be stored under refrigeration for up to 4 weeks. See Appendix A for product characteristics comparison of the LD Cozaar and the proposed Arbli.

During the previous review cycle, the Applicant originally proposed (b) (4) After discussion with the Office of Pharmaceutical Quality (OPQ) and the DCN clinical review team, we recommended that the Applicant remove (b) (4) The Applicant agreed to remove (b) (4) Section 17 of the PI contains the statement "Instruct patients or caregivers to use oral dosing syringe(s) or an oral dosing cup to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringe(s) or an oral dosing cup may be obtained from their pharmacy."

The Applicant originally proposed (b) (4) . For accuracy, we will request that reference to the (b) (4) be removed from the PI. In addition, we will recommend adding "once daily" to the dose increase in hypertensive patients with left ventricular hypertrophy and "orally once daily" to the starting dose to treat adult hypertension.

We reached out to the Office of Pharmaceutical Quality (OPQ) to clarify if the product has a different expiration date after opening. OPQ indicated that the Applicant provided in-use stability data demonstrating that the drug remains within specification for 60 days after use. Since Arbli must be dispensed in the original container and the 165 mL bottle may provide more than a 60 day supply for some patients, we will recommend adding instructions in Section 16 of the PI, the container label, and carton labeling to discard the drug after 60 days of use. In addition, we will recommend space for end-users to write the beyond-use date on the container label and carton labeling.

Lastly, we note that the container label uses the expiration date format of "YYYY-MM-DD" while the carton labeling uses the expiration date format of "YYYY-MMM-DD". We will request the Applicant to clarify if the intent is to only use numerical characters on the container label while using alphabetical characters to represent the month on the carton labeling, or if the expiration date format will be updated to be consistent between the container label and carton labeling.

4 CONCLUSION

The proposed Arbli Prescribing Information (PI), container label, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Cardiology and Nephrology (DCN) in Section 5 and for Scienture LLC in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. Highlights of Prescribing Information

    a. As currently presented in Dosage and Administration, Hypertensive Patients with Left Ventricular Hypertrophy, second bullet point, the statement (b) (4) . We recommend revising the statement "… increase Arbli to 100 mg orally followed by…" to read "… increase Arbli to 100 mg orally once daily followed by…"

    b. As currently presented, it states "See 17 for PATIENT COUNSELING INFORMATION (b) (4) Since it was determined that (b) (4) we recommend removing the statement (b) (4) for accuracy.

2. Section 2 Dosage and Administration

    a. As currently presented in section 2.2 Hypertension, Adult Hypertension, the statement "A starting dose of 25 mg is recommended…" does not include the route of administration and frequency of administration. Failure to include this information may lead to wrong route of administration errors or wrong frequency of administration errors. We recommend revising the statement "A starting dose of 25 mg is recommended…" to read "A starting dosage of 25 mg orally once daily is recommended…"

3. Section 16 How Supplied/Storage and Handling

    a. As currently presented, there is no information indicating that the product should be discarded after 60 days of use. Not including this information may lead to deteriorated drug medication errors. We recommend adding a statement to discard the product after 60 days of use.

6 RECOMMENDATIONS FOR SCIENTURE LLC

A. General Comments (Container Label and Carton Labeling)

1. As currently presented, there is no information indicating that the product should be discarded after 60 days of use. Not including this information may lead to deteriorated drug medication errors. We recommend adding a statement to discard the product after 60 days of use. In addition, since the product has a different expiration date after opening, the container label and carton labeling should have a designated space and format for end-users to write the beyond-use date to minimize the risk of deteriorated drug medication errors. We recommend including space for end-users to write the beyond-use date on the container label and carton labeling. For example:

   Discard after ___/____/____

2. The container label uses the expiration date format of "YYYY-MM-DD" while the carton labeling uses the expiration date format of "YYYY-MMM-DD". We are unable to assess the proposed expiration date format from a medication safety perspective without further information. Please clarify if the intent is to use numerical characters to represent the month on the container label and use alphabetical characters to represent the month on the carton labeling, or if the expiration date format will be updated to be consistent between the container label and carton labeling. If the later, please specify which expiration date format will be used for both the container label and carton labeling. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. *See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Arbli received on October 1, 2024 from Scienture LLC, and the Listed Drug (LD).

Table 2. Relevant Product Information for Arbli and the Listed Drug (LD).		
Product Name	Arbli	Cozaar[f] (NDA 020386)
Initial Approval Date	N/A	April 14, 1995
Active Ingredient	losartan potassium	losartan potassium
Indication	• 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.	• 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.
Dosage Form	oral suspension	tablets
Strength	10 mg/mL	25 mg, 50 mg, and 100 mg
Route of Administration	oral	oral

[f] Cozaar [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. October 2021. [cited 2024 DEC 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020386s064lbl.pdf.

Table 2. Relevant Product Information for Arbli and the Listed Drug (LD).		
Product Name	Arbli	Cozaar[f] (NDA 020386)
Dose and Frequency	Hypertension *Adult Hypertension* The usual starting dose of Arbli is 50 mg orally once daily. The dosage can be increased to a maximum dose of 100 mg orally once daily as needed to control blood pressure. A starting dose of 25 mg is recommended for patients with possible intravascular depletion (e.g., on diuretic therapy). *Pediatric Hypertension* The usual recommended starting dose is 0.7 mg per kg orally once daily (up to 50 mg total) administered as a suspension. Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg per kg (or in excess of 100 mg) daily have not been studied in pediatric patients. Arbli is not recommended in pediatric patients less than 2 years of age or in pediatric patients with estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 Hypertensive Patients with Left Ventricular Hypertrophy The usual starting dose is 50 mg of Arbli orally once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of Arbli should be increased to 100 mg orally once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response. Nephropathy in Type 2 Diabetic Patients The usual starting dose is 50 mg orally once daily. The dose should be	Hypertension *Adult Hypertension* The usual starting dose of COZAAR is 50 mg once daily. The dosage can be increased to a maximum dose of 100 mg once daily as needed to control blood pressure. A starting dose of 25 mg is recommended for patients with possible intravascular depletion (e.g., on diuretic therapy). *Pediatric Hypertension* The usual recommended starting dose is 0.7 mg per kg once daily (up to 50 mg total) administered as a tablet or a suspension. Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg per kg (or in excess of 100 mg) daily have not been studied in pediatric patients. COZAAR is not recommended in pediatric patients less than 6 years of age or in pediatric patients with estimated glomerular filtration rate less than 30 mL/min/1.73 m^2. Hypertensive Patients with Left Ventricular Hypertrophy The usual starting dose is 50 mg of COZAAR once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of COZAAR should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response. Nephropathy in Type 2 Diabetic Patients The usual starting dose is 50 mg once daily. The dose should be increased to

<table>
<tr><th colspan="3">Table 2. Relevant Product Information for Arbli and the Listed Drug (LD).</th></tr>
<tr><td>Product Name</td><td>Arbli</td><td>Cozaar[f] (NDA 020386)</td></tr>
<tr><td></td><td>increased to 100 mg orally once daily based on blood pressure response.
Dosage Modifications in Patients with Hepatic Impairment
In patients with mild-to-moderate hepatic impairment the recommended starting dose of Arbli is 25 mg orally once daily. Arbli has not been studied in patients with severe hepatic impairment.</td><td>100 mg once daily based on blood pressure response.
Dosage Modifications in Patients with Hepatic Impairment
In patients with mild-to-moderate hepatic impairment the recommended starting dose of COZAAR is 25 mg once daily. COZAAR has not been studied in patients with severe hepatic impairment.</td></tr>
<tr><td>How Supplied</td><td>Arbli (losartan potassium) is a white, translucent oral suspension (b) (4) 10 mg of losartan potassium per mL. It is supplied as 165 mL in a high-density polyethylene (HDPE) bottle with a child-resistant cap and tamper-evident seal. Shake for 20 seconds prior to each use.
NDC 83245-053-06</td><td>COZAAR is a white film-coated tablet supplied as follows:<table><tr><th rowspan="2">Losartan</th><th rowspan="2">Shape</th><th rowspan="2">Engraving (reverse)</th><th colspan="2">NDC 78206-xxx-xx</th></tr><tr><th>Bottle/30</th><th>Bottle/90</th></tr><tr><td>25 mg</td><td>oval</td><td>951</td><td>n/a</td><td>121-01</td></tr><tr><td>50 mg</td><td>oval</td><td>952 (scored)</td><td>122-01</td><td>122-02</td></tr><tr><td>100 mg</td><td>teardrop</td><td>960</td><td>123-01</td><td>123-02</td></tr></table></td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.
Store and dispense in original container.</td><td>Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.</td></tr>
<tr><td>Container Closure</td><td>6 ounces white HDPE bottle with (b) (4) cap with liner</td><td>75 mL, 30-count or 90-count, HDPE bottle with white polypropylene, continuous threaded 33 mg CR closure with pulp and polyethylene liner</td></tr>
</table>

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Arbli labels and labeling submitted by Scienture LLC.

- Prescribing Information received on October 1, 2024, available from \\CDSESUB1\EVSPROD\nda218772\0027\m1\us\1-14-2-2-final-package-insert-pdf.pdf
- Container label received on October 1, 2024
- Carton labeling received on October 1, 2024

B.2 Container Label and Carton Labeling Images

Container Label:

(b) (4)

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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APPENDIX C. PREVIOUS DMEPA REVIEWS

On December 10, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, '218772' and 'losartan'. Our search identified two previous reviews[h,i] , and we considered our previous recommendations to see if they are applicable for this current review.

[h] Kundreskas, J. Review of Revised Label and Labeling for Arbli (NDA 218772). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUL 29. TTT ID No.: 2023-6874-1.

[i] Kundreskas, J. Label and Labeling Review for Arbli (NDA 218772). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUL 08. TTT ID No.: 2023-6874.

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/s/

JULIE V NESHIEWAT
02/18/2025 12:32:28 PM

NICOLE F IVERSON
02/18/2025 02:12:00 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 7, 2025

To: Sabry Soukehal, Senior Regulatory Health Project Manager
The Division of Cardiology and Nephrology (DCN)

Michael Monteleone, MS, RAC
Associate Director for Labeling, DCN

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ARBLI (losartan potassium) oral suspension, for oral use

NDA: 218772

Background:

In response to DCN's consult request dated December 11, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton/container labeling for the NDA resubmission for ARBLI (losartan potassium) oral suspension, for oral use.

PI
OPDP's review of the proposed PI is based on the draft labeling e-mailed to OPDP on January 29, 2025, and we do not have any comments.

Carton and Container Labeling:
OPDP has reviewed the attached proposed carton and container labeling submitted to the electronic document room on October 1, 2024, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 29, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 218772
Product Name, Dosage Form, and Strength:	Arbli (losartan potassium) oral suspension, 10 mg/mL
Applicant Name:	Scienture Inc.
FDA Received Date:	July 24, 2024
TTT ID #:	2023-6874-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Scienture Inc. submitted revised container label and carton labeling received on July 24, 2024 for Arbli. We reviewed the revised container label and carton labeling for Arbli (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Scienture Inc. implemented all of our recommendations and we have no additional recommendations at this time.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Kundreskas, J. Label and Labeling Review for Arbli (NDA 218772). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUL 03. TTT ID: 2023-6874.

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/s/

JODY K KUNDRESKAS
07/29/2024 10:52:00 AM

NICOLE F IVERSON
07/29/2024 04:24:56 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 3, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 218772
Product Name, Dosage Form, and Strength:	Arbli (losartan potassium) oral suspension, 10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Scienture Inc.
FDA Received Date:	October 19, 2023, January 15, 2024, May 9, 2024, May 28, 2024, and June 20, 2024
TTT ID #:	2023-6874
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Arbli (losartan potassium) oral suspension, we reviewed the proposed Arbli Prescribing Information (PI), (b) (4) container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Arbli (losartan potassium) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Cozaar (losartan potassium), NDA 020386.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 218772.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Information Request	D

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), container label, and carton labeling for Arbli to identify deficiencies that may lead to medication errors and other areas of improvement. The Division of Cardiology and Nephrology determined that a (b) (4) .

We note that the proposed Arbli oral suspension has the same active ingredient (losartan potassium), indications, recommended dosage, and route of administration (oral) as the Listed Drug (LD), Cozaar. However, there are differences between the proposed product and the LD in dosage form and packaging. The proposed product will be available in a 165 mL bottle of a 10 mg/mL oral suspension whereas the LD is approved as 25 mg, 50 mg, and 100 mg tablets. Additionally, we note that the LD labeling includes instructions for the preparation of a 200 mL bottle of a 2.5 mg/mL oral suspension utilizing ten 50 mg tablets which can be stored under refrigeration for up to 4 weeks. See Appendix A for product characteristics comparison of the LD Cozaar and the proposed Arbli.

We note that the Applicant proposed to provide (b) (4)

[a] Container Closure System for NDA 218772, Losartan Potassium Oral Suspension 10 mg/mL. Commack (NY): Scienture Inc.; 2023 OCT 19. Available from: \\CDSESUB1\EVSPROD\nda218772\0001\m3\32-body-data\32p-drug-prod\losartan-oral-suspension\32p7-cont-closure-sys\32p7-cont-clos-sys.pdf.

4 CONCLUSION

The proposed Arbli Prescribing Information (PI), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed

[b] Information Request Response for Arbli (NDA 218772). Commack (NY): Scienture Inc.; 2024 MAY 09. Available from: \\CDSESUB1\EVSPROD\nda218772\0014\m1\us\1-2-cover-letter-esigned.pdf.

[c] Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors. Food and Drug Administration. 2016. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf.

[d] Information Request Response for Arbli (NDA 218772). Commack (NY): Scienture Inc.; 2024 JUN 20. Available from: \\CDSESUB1\EVSPROD\nda218772\0016\m1\us\1-2-cover-letter-pdf.

recommendations to minimize the risk for medication error for the Division of Cardiology and Nephrology (DCN) in Section 5 and for Scienture Inc. in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. General Comments
    a. As currently presented, the proprietary name is denoted by the placeholder "Tradename". We reference our January 22, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Arbli, was found conditionally acceptable. We recommend replacing the placeholder "Tradename" with the conditionally acceptable proprietary name, Arbli.
2. Highlights of Prescribing Information
    a. The route of administration is missing in the Dosage and Administration Section. Failure to include the route of administration may lead to wrong route errors. We recommend adding the route of administration "orally" to each recommended dosage.
3. Section 2 Dosage and Administration
    a. The route of administration is not present. Failure to include the route of administration may result in wrong route errors. In the Dosage and Administration Section, we recommend adding the route of administration, "orally", to each recommended dosage.
    b. As currently presented, Section 2 of the PI does not contain a statement instructing patients and/or caregivers to use an oral dosing syringe to measure the prescribed dose. Evidence suggests that use of oral syringes may decrease the risk of wrong dose error.[e] We recommend adding Section 2.1 *Important Administration Information* and including the following statements in this section: "Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy.".
4. Section 16 How Supplied/Storage and Handling
    a. The statement, "Store and dispense in original container" is listed on the carton labeling and container label but missing from the Prescribing Information (PI). Lack of this instruction in the PI may lead to dispensing errors. We recommend adding the statement, "Store and dispense in original container" to the end of Section 16.
    b. The unit of measure is missing from some of the temperature references. Unclear storage information may lead to confusion and potential risk of deteriorated drug medication errors. We recommend adding the unit of

[e] Institute for Safe Medication Practices. 2010 FEB. In The News… Parents' dosing accuracy. ISMP Med Saf Alert Community/Ambulatory Care. 9(2):3.

measure after each numerical degree. Revise “Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].” to “Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].”.

c. The handling instruction [redacted] (b) (4) can be revised to improve clarity. We recommend revising to “Shake for 20 seconds prior to each use.”.

d. The net quantity statement “It is supplied as 165 mL in a 6-ounce high-density polyethylene (HDPE) bottle with a child-resistant cap and tamper-evident seal.” may cause confusion as it uses the apothecary system (ounce) and contains unnecessary information about the size of the empty bottle. We recommend presenting the net quantity statement in metric units (e.g., mL) only, without the empty bottle size. For added clarity, we recommend revising the net quantity statement to “It is supplied as 165 mL in a high-density polyethylene (HDPE) bottle with a child-resistant cap and tamper-evident seal.”.

5. Section 17 Patient Counseling

a. As currently presented, Section 17 of the PI does not contain a statement instructing patients and/or caregivers to use an oral dosing syringe to measure the prescribed dose. Evidence suggests that use of oral syringes may decrease the risk of wrong dose error.[f] We recommend adding a section entitled *Administration Information* and including the following statements in that section: “Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy.”.

6 RECOMMENDATIONS FOR SCIENTURE INC.

A. General Comments (Container Label & Carton Labeling)

1. As currently presented, the proprietary name is denoted by the placeholder “Tradename”. We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our January 22, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Arbli, was found conditionally acceptable. We recommend replacing the placeholder “Tradename” with the conditionally acceptable proprietary name, Arbli, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.

[f] Institute for Safe Medication Practices. 2010 FEB. In The News… Parents’ dosing accuracy. ISMP Med Saf Alert Community/Ambulatory Care. 9(2):3.

2. The “Rx only” statement appears more prominent than other critical information (e.g., proprietary name, established name, strength) on the principal display panel. The “Rx only” statement should not compete in size and prominence with critical information on the principal display panel. We recommend debolding the “Rx only” statement so that it does not compete in size or prominence with critical information on the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3. The terminology within the statement of dosage statement (b) (4) is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the statement of dosage statement to read, “Recommended Dosage: See Prescribing Information.”.
4. Most of the information on the side panel is presented in bold font and appears prominent. Bolding most of the information on the side panel may cause important information to be overlooked. We recommend you consider decreasing the prominence of “Each 1 mL contains:”, “Recommended Dosage:” and “Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].” through debolding.
5. The unit of measure is missing from some of the temperature references. Unclear storage information may lead to confusion and potential risk of deteriorated drug medication errors. We recommend adding the unit of measure after each numerical degree. Revise “Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].” to “Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].”.
6. The statement, “Shake for 20 seconds before each use” is missing from the Principal Display Panel (PDP). This instruction is in the Prescribing Information, and lack of this instruction on the carton labeling and container label may lead to administration errors. Add “Shake for 20 seconds before each use” to the PDP.
7. As currently presented. the net quantity statement contains an error prone abbreviation, “oz” and uses both the metric and apothecary systems of measurement.[g] The abbreviation “oz” can be misinterpreted as a zero or 02. We recommend expressing the net quantity statement in metric units (e.g., mL) only.
8. We note that the format for the expiration date “YYYY-MMM-DD” is in the lot number placeholder. We request clarification on the presentation of the lot number and the location of the expiration date so that we can assess this information from a medication safety perspective.

[g] ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2024 [cited 2024 JUN 03]. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf.

B. Carton Labeling

1. As currently presented, the large blue and green geometric graphic beneath the strength statement competes with the prominence of the proprietary name, established name, and strength on the Principal Display Panel (PDP). The proprietary name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. Decrease the prominence of your graphic relative to the prominence of the proprietary name, established name, and strength on the PDP needed for proper identification and use of your proposed product in accordance with 21 CFR 201.15(a)(6). For example, this may be accomplished through increasing the prominence of the critical information and/or minimizing the graphic itself or moving it to another panel.
2. The product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.
3. This product should be dispensed with an oral dosing syringe to correctly measure the prescribed amount of medication. We recommend placing a warning statement on the carton labeling stating "Pharmacist: Dispense appropriately sized oral syringe(s) per the determined dosing regimen prescribed.".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Arbli received on May 28, 2024 from Scienture Inc., and the Listed Drug (LD).

Table 2. Relevant Product Information for Arbli and the Listed Drug (LD).		
Product Name	Arbli	Cozaar[h]
Initial Approval Date	N/A	April 13, 1995
Active Ingredient	losartan potassium	
Indication	For the treatment of hypertension in adults and pediatric patients 6 years of age and older, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and nonfatal cardiovascular (CV) events, primarily strokes and myocardial infarction.	
Dosage Form	oral suspension	tablets
Strength	10 mg/mL	25 mg, 50 mg, and 100 mg
Route of Administration	oral	

[h] Cozaar [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. October 2021. [cited 2024 APR 04]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020386s064lbl.pdf.

Table 2. Relevant Product Information for Arbli and the Listed Drug (LD).		
Product Name	Arbli	Cozaar[h]
Dose and Frequency	• Hypertension Adult Hypertension: The usual starting dose is 50 mg once daily. The dosage can be increased to a maximum dose of 100 mg once daily as needed to control blood pressure. A starting dose of 25 mg is recommended for patients with possible intravascular depletion (e.g., on diuretic therapy). Pediatric Hypertension: The usual recommended starting dose is 0.7 mg per kg once daily (up to 50 mg total) administered as a suspension. Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg per kg (or in excess of 100 mg) daily have not been studied in pediatric patients. TRADENAME is not recommended in pediatric patients less than 6 years of age or in pediatric patients with estimated glomerular filtration rate less than 30 mL/min/1.73 $m^{2.}$ • Hypertensive Patients with Left Ventricular Hypertrophy The usual starting dose is 50 mg once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of TRADENAME should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide	• Hypertension Adult Hypertension: The usual starting dose is 50 mg once daily. The dosage can be increased to a maximum dose of 100 mg once daily as needed to control blood pressure. A starting dose of 25 mg is recommended for patients with possible intravascular depletion (e.g., on diuretic therapy). Pediatric Hypertension: The usual recommended starting dose is 0.7 mg per kg once daily (up to 50 mg total) administered as a tablet or a suspension. Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg per kg (or in excess of 100 mg) daily have not been studied in pediatric patients. COZAAR is not recommended in pediatric patients less than 6 years of age or in pediatric patients with estimated glomerular filtration rate less than 30 mL/min/1.73 $m^{2.}$ • Hypertensive Patients with Left Ventricular Hypertrophy The usual starting dose is 50 mg once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of COZAAR should be increased to 100 mg once daily followed by an increase in

Table 2. Relevant Product Information for Arbli and the Listed Drug (LD).		
Product Name	Arbli	Cozaar[h]
	to 25 mg once daily based on blood pressure response. • Nephropathy in Type 2 Diabetic Patients The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response. • Dosage Modifications in Patients with Hepatic Impairment In patients with mild-to-moderate hepatic impairment the recommended starting dose is 25 mg once daily. TRADENAME has not been studied in patients with severe hepatic impairment.	hydrochlorothiazide to 25 mg once daily based on blood pressure response. • Nephropathy in Type 2 Diabetic Patients The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response. • Dosage Modifications in Patients with Hepatic Impairment In patients with mild-to-moderate hepatic impairment the recommended starting dose is 25 mg once daily. COZAAR has not been studied in patients with severe hepatic impairment.
How Supplied	TRADENAME (losartan potassium) is a white, translucent oral suspension that contains 10 mg of losartan potassium per mL. It is supplied as 165 mL in a 6-ounce high-density polyethylene (HDPE) bottle with a child-resistant cap and tamper-evident seal. Shake for 20 seconds. NDC 83245-053-06	COZAAR is a white film-coated tablet supplied as follows: • 25 mg: Bottle of 90 • 50 mg: Bottle of 30 and bottle of 90 • 100 mg: Bottle of 30 and bottle of 90
Storage	Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.

Table 2. Relevant Product Information for Arbli and the Listed Drug (LD).		
Product Name	Arbli	Cozaar[h]
Container Closure	HDPE bottles 6 oz Round White and Polypropylene Cap with liner.	30 or 90 count white polypropylene bottles

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Arbli labels and labeling submitted by Scienture Inc..

- Prescribing Information received on May 28, 2024, available from \\CDSESUB1\EVSPROD\nda218772\0015\m1\us\1-14-2-2-draft-package-insert-pdf.pdf
- Container label(s) received on October 19, 2023
- Carton labeling received on October 19, 2023

B.2 Container Label(s) and Carton Labeling Images

Container label:

(b) (4)

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 2, 2024

To: Silvia (Sarai) Bartlett, Regulatory Health Project Manager
The Division of Cardiology and Nephrology (DCN)

Michael Monteleone, MS, RAC
Associate Director for Labeling, DCN

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (losartan potassium) oral suspension, for oral use

NDA: 218772

Background:

In response to DCN's consult request dated November 22, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and carton/container labeling for the original NDA submission for losartan potassium oral suspension, for oral use.

PI
OPDP's review of the proposed PI is based on the draft labeling downloaded from SharePoint on June 27, 2024, and are comments are below.

Carton and Container Labeling:
OPDP has reviewed the attached proposed carton and container labeling downloaded from SharePoint on June 27, 2024, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
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M E M O R A N D U M

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

DATE: May 30, 2024

TO: Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiology and Nephrology (DCN)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs (OND)

Partha Roy, Ph.D.
Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Makini Cobourne-Duval, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Remote Regulatory Assessment (RRA) of (b) (4) (b) (4)

1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA) of the analytical portion of study 14323/21-22 (NDA 218772, losartan potassium), (b) (4) (b) (4) (b) (4).

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. There were no items discussed at the inspection close-out. Based on the inspection findings, there are no identified concerns for (b) (4) regarding reliability of the data for inspected study 14323/21-22 (NDA 218772), (b) (4) (b) (4)

2. Reviewed Studies:

NDA 218772

Study Number: 14323/21-22 (fasting)
Study Title:
"An open label, balanced, randomized, single oral dose, two-treatment, two-sequence, four-period, fully replicate, crossover study to assess the relative bioavailability of Losartan Potassium 10 mg/mL of oral Liquid (10 mL with a total dose of 100 mg) (T) with COZAAR® (losartan potassium) tablets 100 mg (R) in healthy adult study participants under fasting conditions."
Sample Analysis Period: 12/29/2022 – 01/20/2023

(b) (4)

(b) (4)

(b) (4)
(b) (4)

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3. RRA Findings

(b) (4)

OSIS scientist Makini Cobourne-Duval, Ph.D. reviewed analytical portion of the above studies conducted at (b) (4) (b) (4).

(b) (4)

(b) (4)

3.2 Current Inspection

The current RRA included examination the following items:

-Relevant site facilities and analytical areas
-Relevant laboratory instrument calibration and maintenance
-Standard Operating Procedures (SOPs) and Standard Testing Procedures (STPs) relevant to analytical operations
-Records and processes for method validation and study sample analyses
-Source (raw) data from the analytical instruments
-Biological samples receipt, storage, tracking, and accountability records
-Sample processing records
-Interviews with the firm's management and staff

3.3 Inspection findings

At the conclusion of the RRA, I did not observe any objectionable conditions. I did not issue Form FDA 483 to the analytical site and there were no items discussed with the firm's management during the RRA close-out meeting.

Makini Cobourne-Duval, Ph.D.
Pharmacologist

Draft: MCD 05/23/2024
Edit: MO 05/24/2024; JC 05/24/2024

OSIS File #: BE (b) (4) (NDA 218772) (b) (4)

eNSpect Assignment ID: (b) (4)
eNSpect OpID: (b) (4)

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/s/

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