CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212304Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: February 25, 2022

To: Brian Trummer, MD, PhD, Clinical Reviewer
Division of Neurology I (DN1)

Justine Kankam, PharmD, Regulatory Health Project Manager, (DN1)

Tracy Peters, PharmD, Associate Director for Labeling, (DN1)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ADLARITY® (donepezil transdermal system)

NDA: 212304

In response to DN1's consult request dated January 28, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for ADLARITY® (donepezil transdermal system), (Adlarity).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN1 (Justine Kankam) on February 11, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on February 24, 2022.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 4, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

REBECCA A FALTER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 24, 2022
To:	Justine Kankam, PharmD Regulatory Health Project Manager **Division of Neurology I (DN1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nydra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Office **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ADLARITY (donepezil transdermal system)
Dosage Form and Route:	transdermal system (TDS)
Application Type/Number:	NDA 212304
Applicant:	Corium Inc.

1 INTRODUCTION

On September 10, 2021, Corium Inc, submitted for the Agency's review a Class 2 Resubmission to their original New Drug Application (NDA) 212304 for ADLARITY (donepezil transdermal system). This 505(b)(2) Application was submitted in response to the Agency's Complete Response Letter issued on July 23, 2020 due to clinical deficiencies. With this submission, the Applicant is proposing an indication for the treatment of mild, moderate and severe dementia of the Alzheimer's type.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN1) on January 28, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ADLARITY (donepezil transdermal system).

2 MATERIAL REVIEWED

- Draft ADLARITY (donepezil transdermal system) PPI and IFU] received on September 10, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 11, 2022.
- Draft ADLARITY (donepezil transdermal system) Prescribing Information (PI) received on September 10, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 11, 2022.
- Approved ARICEPT (donepezil hydrochloride) comparator dated labeling December 18, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU documents using the Arial font, size 10 and 11 respectively.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

MARY E CARROLL
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SHARON W WILLIAMS
02/24/2022 01:16:10 PM

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: 2/18/2022

TO: Division of Neurology I (DN I)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212304

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the clinical site in October 2018. The inspection was conducted under the following submissions: ANDAs NON-RESPONSIVE.

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observation:

- For ANDA NON-RESPONSIVE only, one subject in Study NON-RESPONSIVE was enrolled and dosed with study drug but should have been excluded from the study based on the protocol exclusion criteria.

After receiving a written response from the site, OSIS determined that the site adequately addressed the above concern and recommended all study date be accepted for review (OSIS Final Review – October 2018).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Worldwide Clinical Trials (WCT) Early Phase Services, LLC.	2455 Northeast Loop 410, Suite 150, San Antonio, TX

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/s/

NICOLA M FENTY-STEWART
02/18/2022 09:31:37 AM

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)

Date of This Memorandum:	February 10, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 212304
Product Name and Strength:	Adlarity (donepezil transdermal system), 5 mg/day, 10 mg/day
Applicant/Sponsor Name:	Corium, Inc.
OSE RCM #:	2019-2155-2
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, carton labeling, and system backing received on January 19, 2022 for Adlarity. The Division of Neurology 1 (DN 1) requested that we review the revised labeling for Adlarity (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

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Morris, C. Label and Labeling Review for Adlarity (NDA 212304). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2021 DEC 10. RCM No.: 2019-2155-1.

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STEPHANIE L DEGRAW
02/10/2022 10:41:48 AM

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:	December 10, 2021
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 212304
Product Name and Strength:	Adlarity (donepezil transdermal system), 5 mg/day, 10 mg/day
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Corium, Inc. (Corium)
FDA Received Date:	September 13, 2021
OSE RCM #:	2019-2155-1
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

Corium submitted a Class 2 Resubmission to address deficiencies cited in a complete response letter on July 23, 2020 for Adlarity (donepezil transdermal system)[a]. The Division of Neurology 1 (DN 1) requested that we review the proposed Adlarity Prescribing Information (PI), Patient Information (PPI), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 212304 is a 505(b)(2) NDA and the listed drug product is Aricept, NDA 020690.

Corium submitted the original NDA 212304 on September 30, 2019, and we performed a label and labeling review of the submission during that review cycle[b]. Our recommendations were sent to Corium during that review cycle. However, the application received a complete response (CR) on July 23, 2020.

Therefore, on September 13, 2021, Corium submitted a Class 2 Resubmission to address CR letter deficiencies. The submission included revised labels and labeling, which are the subject of this review.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

[a] July 23, 2020 CR letter available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8057ff36&_afrRedirect=1522524509179480

[b] Baugh, D. Label and Labeling Review for Adlarity (donepezil transdermal system) (NDA 212304). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 16. RCM No.: 2019-2155.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, PPI, IFU container labels, and carton labeling may be improved to promote the 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 in Section 4 for the Division and in Section 5 for Corium, Inc.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	The dosing in the Highlights of the PI, does not state whether it represents the starting dose or the maintenance dose.	The lack of clarity may contribute to wrong dose medication errors	We recommend clarifying whether the dosing in the Highlights refers to the starting dose or maintenance dose.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	(b) (4)		We defer to the review team whether duplicating this information is necessary.
2.	Sections 2.1, 2.2, and 2.3 contain the "-" symbol.	Symbols may be misinterpreted.	We recommend revising "-" to the intended meaning "to".
3.	In Section 2.4, the step which states "Allow the pouch to reach room	This does not follow the order of the use of the product.	We recommend making the instruction "Allow the pouch to reach room temperature

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	temperature before opening" appears in the middle of the second bullet point.		before opening" its own step and relocating it to the first bullet point. We also recommend adding a statement not to apply external heat sources to warm the patch. Please assure this information is presented consistently throughout Sections 2 and 17 of the PI, the PPI, and IFU.
4.	Section 2.4 does not instruct the user what to do if the patch falls off.	May increase the risk for degraded drug medication errors.	We recommend adding the following language from the IFU to Section 2.4, "(b) (4) [redacted]" Please assure this information is presented consistently throughout Sections 2 and 17 of the PI, the PPI, and IFU.
5.	The effect of showering is not addressed is not addressed in Section 2.4.	May increase the risk for unnecessary removal.	We recommend adding the following language from the IFU to Section 2.4, "(b) (4) [redacted]". Please assure this information is presented consistently throughout Sections 2 and 17 of the PI, the PPI, and IFU.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Full Prescribing Information – Section 16 How Storage and Handling and Section 17 Patient Counseling Information **Patient Information – What should I avoid while using Adlarity?** **Instructions for Use - [redacted](b) (4), How to [redacted](b) (4) store Adlarity, and Step 2: Removing the Adlarity [redacted](b) (4) from the pouch**			
1.	The instructions for allowing the patch to reach room temperature can be improved for clarity.	We are concerned the user may heat the patch to bring it to room temperature.	We recommend adding a statement not to apply external heat sources to warm the patch.
Instructions for Use – Step 1: Where to apply the Adlarity patch			
1.	The illustration of acceptable application sites can be improved.	The illustration identifying possible locations for the patch may be misinterpreted to mean that a patch should be applied to more than one site, which may result in an overdose	We recommend considering the labeling of other transdermal systems to determine how to best accomplish this, which may include prominent statements such as, Only 1 patch should be worn at a time. Do not apply multiple patches to the body.

5 RECOMMENDATIONS FOR CORIUM, INC.

Table 3. Identified Issues and Recommendations for Corium, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label(s) and Carton Labeling			
1.	Refrigeration is a new storage condition for a patch in the indicated population.	We are concerned users may store the patch at room temperature leading to degraded drug medication errors.	We recommend increasing the prominence of the storage statement (i.e., increase the font size and use bolded font). Additionally, consider adding a storage statement warning in a

Table 3. Identified Issues and Recommendations for Corium, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			prominent location of the PDP such as, “Store in refrigerator” or similar.
2.	The established name is not at least half the size of the proprietary name.	The established name is not presented in accordance with 21 CFR 201.10(g)(2).	We recommend you increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3.	The strength statement appears twice on the principal display panel (PDP), one of which includes dosing information ((b) (4) .	Duplicating the strength statement is unnecessary and creates clutter.	We recommend you present the strength statement only once, as “xx mg/day”, on the PDP. If you intend to present dosing information on the PDP, we recommend you consider adding it beneath the route of administration statement, such as: “For Transdermal Use Only” “For Once Weekly Administration” or similar.
4.	The strength statement (that is, xx mg/day) on the PDP is not prominent and may be difficult to read.	We are concerned the strength may be overlooked, and may increase the risk for wrong strength medication errors.	To improve prominence and readability of the strength statement, we recommend you relocate the strength statement to the middle of the PDP and improve its readability by considering font size, formatting, color, and contrast.
5.	The format for the expiration date is not defined.	We are unable to assess the risk for medication errors	Identify the format you intend to use. We recommend the human-readable expiration

Table 3. Identified Issues and Recommendations for Corium, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		with the expiration date format.	date on the product package label include a year, month, and non-zero day. We recommend 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. If there are space limitations on the product package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. Please specify whether the month portion of the expiration date will be alphabetical or numerical. A hyphen or a space may be used to separate the three portions of the expiration date. Ensure that there are no other numbers located in close proximity to the expiration date, which may be mistaken as the expiration date.
Container Labels			
1.	The linear barcode is more prominent than other important information.	The linear barcode may detract the user from differentiating strengths or understanding other	While still ensuring scannability of the barcode, we recommend you display the linear barcode with commensurate

Table 3. Identified Issues and Recommendations for Corium, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		important information such as the "avoid applying heat" warning statement.	prominence to other important information on the label.
2.	The patch backing labeling was not submitted.	We are unable to assess from a medication error perspective.	Please submit the proposed patch surface labeling with representative backing and print color for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Adlarity that Corium, Inc. submitted on September 13, 2021, and Aricept.

Table 4. Relevant Product Information for Listed Drug and Adlarity		
Product Name	Aricept [c]	Adlarity
Initial Approval Date	11/25/1996	n/a
Active Ingredient	Donepezil hydrochloride	donepezil
Indication	(b) (4)	
Route of Administration	Oral	Transdermal
Dosage Form	Tablet	Transdermal system
Strength	5 mg, 10 mg, 23 mg	5 mg/day, 10 mg/day
Dose and Frequency	Mild to moderate AD: 5 mg or 10 mg once daily Moderate to severe AD: (b) (4) 10 mg, or 23 mg once daily	One 5 mg/day patch once weekly, may increase to one 10 mg/day patch once weekly after 4 weeks to 6 weeks

[c] Link to Aricept PI, accessed 11/16/2021:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf

How Supplied	5 mg and 10 mg: bottles of 30 and 90 and unit dose blister pack of 100 tablets 23 mg: bottles of 30 tablets	Carton containing 4 individually packaged transdermal systems
Storage	Store at controlled room temperature, 15°C to 30°C (59°F to 86°F).	Store in the refrigerator between 2°C to 8°C (36°F to 46°F). Do not [(b) (4)]. Allow the pouch to reach room temperature before opening and removing the new [(b) (4)] for application. Keep in the individually sealed pouch until use.
Container Closure	HDPE bottles, foil-backed blisters	[(b) (4)] printed pouch

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 16, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Adlarity, donepezil transdermal system, and NDA 212304. Our search identified two additional reviews, and we considered our previous recommendations to see if they are applicable for this current review.[de]

OSE RCM# 2020-816, June 16, 2020

We reviewed labeling comprehension study results to determine the clarity and effectiveness of the labeling instructions for patch application, patch removal and disposal. We noted, the errors observed are concerning from a medication error perspective as they can result in accidental exposure to active drug, overdose and underdose medication errors. We also noted deficiencies in study methodology. Therefore, we were unable to conclude that the Human Factors Labeling Comprehension Study confirms that the product labeling addresses the risks associated with the separation of (b) (4) the TDS (b) (4). We provided DN1 letter-ready comments for Corium.

OSE RCM# 2019-2155, April 16, 2020

We reviewed the labels and labeling for the original submission. We provided recommendations for DN1 and Corium. The assessment of the revisions associated with that review are the subject of the current review (OSE RCM# 2019-2155-1).

[d] Holquist, C. Label and Labeling Review for Adlarity (donepezil transdermal system) (NDA 212304). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 16. RCM No.: 2020-816.

[e] Baugh, D. Label and Labeling Review for Adlarity (donepezil transdermal system) (NDA 212304). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 16. RCM No.: 2019-2155.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Adlarity labels and labeling submitted by Corium, Inc. on September 13, 2021.

- Trade container labels
- Trade carton labeling
- Professional Sample container labels
- Professional Sample carton labeling
- Prescribing Information, Patient Information, and Instructions for Use (Image not shown), available from \\CDSESUB1\evsprod\nda212304\0028\m1\us\114-labeling\draft\labeling\11413-draft-text-labeling.docx

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

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

DATE: 11/26/2021

TO: Division of Neurology I (DN I)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212304

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submission: NON-RESPONSIVE.

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

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MEMORANDUM

LABELING COMPREHENSION STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 16, 2020
Requesting Office or Division:	Division of Neurology 1 (DN1)
Application Type and Number:	NDA 212304
Product Type:	Combination Product (Drug-Device)
Product Name, Dosage Form, and Strength:	ADLARITY[a] (donepezil transdermal system) 5 mg/day and 10 mg/day
Rx or OTC:	Prescription (Rx)
Applicant Name:	Corium, Inc.
Submission Date:	April 10, 2020
OSE RCM #:	2020-816
DMEPA Human Factors Evaluator:	Carol Holquist, RPh
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

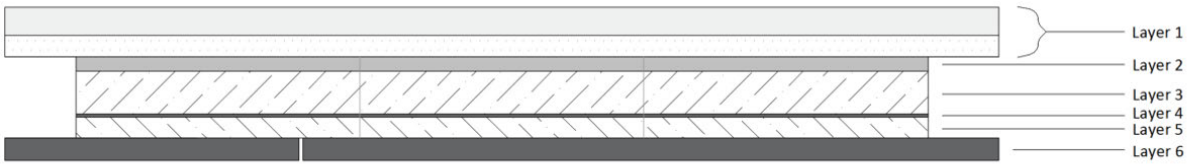
[a] The proposed proprietary name, Adlarity, was found conditionally acceptable in OSE Review #2019-34783352, dated December 17, 2019.

1 PURPOSE OF MEMORANDUM

This memorandum provides our evaluation of the labeling comprehension study results submitted under NDA 212304 for ADLARITY (donepezil transdermal system) to determine the clarity and effectiveness of the labeling instructions for patch application, patch removal and disposal. This combination product with a transdermal system device constituent part is intended to dementia of the Alzheimer's type.

2 PRODUCT DESCRIPTION

ADLARITY (donepezil transdermal system) is a 6-layer laminate rectangular patch with rounded corners containing a tan colored overlay backing/adhesive layer without donepezil, separating layer, drug matrix layer, microporous membrane layer, skin contact adhesive layer, and a peel-off release liner. The release liner is removed and discarded prior to use. ADLARITY is manufactured in two sizes intended to provide an average daily dose of 5 mg or 10 mg donepezil. Each patch is intended to deliver drug for 7 days (1 week) cycle. At the end of 7 days, the used patch is removed, and a new patch is applied. The product is supplied in cartons, with each carton containing four transdermal systems that are individually packaged in sealed pouches.



Layer 1: Overlay Backing/Adhesive
Layer 2: Separating Layer
Layer 3: Drug Matrix
Layer 4: Microporous Membrane
Layer 5: Contact Adhesive
Layer 6: Release Liner (Removed at the time of use)

3 REGULATORY HISTORY

On November 20, 2019, FDA held a telecon with the applicant to discuss an inherent product design flaw with the ADLARITY transdermal system (i.e., risk of separation of (b) (4) the TDS (b) (4)). In response to this teleconference, Corium, Inc. proposed to implement labeling enhancements and to conduct a human factors (HF) labeling comprehension study with the intent to confirm patients and caregivers are able to demonstrate how to safely and effectively apply, remove and dispose of the proposed ADLARITY patch. On January 31, 2020, FDA communicated their concerns to the applicant that "labeling enhancements will not address the inherent product design flaw and the risk of the separation of (b) (4) the TDS (b) (4)" and that a labeling comprehension study is not the appropriate mechanism to address the concerns.[b] Despite this guidance the company conducted the labeling comprehension study dated April 9, 2020

[b] Wheelous, T. Confirmation of Issues Discussed, 2020 JAN 31 e-mail to (b) (4) regarding NDA 212304 Adlarity (donepezil) transdermal Delivery System-November 20, 2019 Discussion. Silver Spring (MD), FDA/CDER/OND/ORO/DN1, 2020 FEB 04. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8053e421&_afrRedirect=773833083393682

submitted April 10, 2020, which is the subject of this review. The Applicant did not provide a HF protocol for Agency review prior to conducting the labeling comprehension study.

Additionally, during the course of our review, we requested ten (10) placebo or active intent-to-market product samples via an information request. In response to the information request, Corium Inc., stated that the Human Factors Study was conducted with Lot 39328B which was not manufactured using the proposed commercial process for the intent-to-market product. The applicant provided samples from ADLARITY TDS, 10 mg/day product lot 39882B, which has a manufacturing date of July 23, 2019, and is representative of intent-to-market product. The applicant stated "(b) (4) ".[c]

4 STUDY DESIGN, METHODOLOGY, AND RESULTS SUMMARY

Corium, Inc. states the objective of the labeling comprehension study was to evaluate the effectiveness of the ADLARITY labeling instructions in preventing/minimizing occurrence of inadvertent use errors during patch application, patch removal and disposal of the patch.

The study was conducted in two stages, Stage 1 and Stage 2. Each stage evaluated the effectiveness of the labeling instructions in the following scenarios:

- Scenario 1: patch application of Baseline Patch (BP) from commercial lot 39328. IFU available but participants were not prompted or required to read them
- Scenario 2: patch removal and disposal of BP patch from Scenario 1
- Scenario 3: patch application with an Altered Baseline Patch (ABP) to intentionally result in Adhesive Square(s) of the patch remaining on liner piece 2 when the liner is being removed. Participants were instructed to read specific sections of the IFU.
- Scenario 4: patch removal and disposal with the BP patch on simulated skin (BPSS) from commercial lot 39328 which was modified to intentionally result in Adhesive Square(s) of the patch remaining on the Simulated Skin when the patch is being removed. Participants were instructed to read specific sections of the IFU.

The only differences between Stage 1 and Stage 2 were changes made to the patch liner and

[c] Corium Inc., Human Factors/Response to Information Request for Adlarity NDA 212304. 2020 MAY 01. Available from: \\cdsesub1\evsprod\nda212304\0019\m1\us\12-cover-letters\cover-letter.pdf

IFU based on Stage 1 findings, the placement of the patch (e.g. use of a mannequin or applied over clothing in stage 1 vs applied to an easel in Stage 2) and the number of participants enrolled in each stage.

4.1 Summary of Stage 1

Eleven participants (n=10 caregivers and 1 patient) were included in Stage 1 of the study. Caregivers applied the patches to simulated skin on a manakin and the patient applied the patches to simulated skin on their pants leg at the thigh. Patch application and patch disposal errors were observed in this formative stage.

Specifically during patch application, study participants removed the larger liner piece 2 before liner piece 1 or removed the liner without using the liner tabs, did not detect remaining adhesive squares (i.e., active segments or squared containing drug) on the liner and did not remove inappropriately applied defective patches from the simulated skin. Patch disposal errors included not discarding the liner in the empty pouch and not appropriately disposing the remaining adhesive squares. Based on these results, several aspects of the user interface were revised before moving to Stage 2. Changes were made to the liner (b) (4) . The (b) (4) and IFU between Stage 1 and Stage 2 were revised to address the use errors, close calls and difficulties observed in Stage 1 simulation and labeling comprehension assessments. The revised IFU and (b) (4) were used in Stage 2 evaluation.

4.2 Summary of Stage 2

Sixteen caregivers (n=16) and seven patients (n=7) participated in Stage 2 of the study using the revised IFU and (b) (4) following completion of Stage 1. Use errors and difficulties were observed in both the simulated use and labeling comprehension assessments.

In the simulated use portion of the study, both caregivers and patients applied the patches to simulated skin that was attached to an abdominal wrap on an easel. Use errors were noted in patch application, patch removal, and patch disposal. Specifically, errors observed include the following:

- Patch Application
    - Removed the larger liner piece 2 before liner piece 1
    - Did not removing the liner using the tabs
    - Applied the patch to the skin with liner 1 still attached to the patch
    - Removing both liner pieces before placing the patch
    - Placed a new patch on top of adhesive squares remaining on the simulated skin
    - Failed to detect adhesive squares remaining on the liner.

- Patch Removal
    - Did not detect and remove remaining adhesive squares on the simulated skin
- Patch Disposal
    - Did not discard the line in the empty pouch
    - Did not appropriately dispose of the remaining adhesive square(s)
    - Did not fold the patch in half before discarding

The root cause of errors observed and gathered in the debriefing for the simulated use tasks included participants not reading the complete IFU or (b) (4) before use, not understanding the (b) (4), not following or seeing the directions in the IFU, not understanding the IFU instructions, and not seeing the adhesive squares on the liner.

During the labeling comprehension portion of the study, one use error occurred when a patient could not correctly describe how to discard remaining adhesive squares that may have been left on skin after reading the instruction. Use difficulties obtained during the labeling comprehension debriefing session revealed the following:

- Confusion with the instructions on how to bend the patch to get the liner to separate and reveal tabs
- Confusing instructions about not touching the patch
- (b) (4)
- Did not understand that adhesive squares were medication segments
- Confusion about what to do if a patch falls off before its time to change it
- Did not understand the images of applying and removing the liner
- Confusion over patch use. Participants requested clarification about using the patch by themselves or if someone else would have to put the patch on their back, how could a patient inspect the patch by themselves if it was placed on his/her back, and confusion over application sites for patients who are applying the patch without assistance from a caregiver.

Based on the participant subjective feedback the root causes of these use difficulties were not understanding images or the text used to describe the task(s), not understanding the difference between terminology (e.g., remaining adhesive squares and remaining residue), and the information not clear enough to know how to proceed if a patch falls off.

5 DISCUSSION AND CONCLUSION

Our review noted the occurrence of similar errors between Stage 1 and 2 which indicates that the labeling revisions implemented prior to Stage 2 did not adequately address the use errors and difficulties observed in Stage 1. The errors observed are concerning from a medication error perspective as they can result in accidental exposure to active drug, overdose and underdose medication errors.

Our review also noted deficiencies with the study methodology. Specifically, the applicant used an inadequate patient sample size (e.g. patient user group included less than 15 participants), the patch application was not representative of actual use (e.g. patches applied on an easel vs. manikin or patient), and the intent-to-market product was not used in the HF labeling comprehension study. Additionally, labeling revisions made following the completion of the Stage 2 were not validated. Corium Inc., stated in the April 10, 2020 submission that "extensive changes were made to the IFU to implement learnings from the labeling comprehension study in an effort to optimize caregiver application, removal and disposal of Adlarity" and that "changes include revised language as well as formatting and orientation to improve readability".[d] However, the labeling comprehension study report does not indicate that these revisions were evaluated to demonstrate that the revised labeling effectively addressed the errors noted in the Stage 2 evaluation and that these proposed labeling changes do not introduce new risks. Thus, these deficiencies not only raise concerns with the study methodology but also impact the acceptability of the submitted data results.

Additionally, the errors observed in this study indicate patients and caregivers do not adequately understand the risks of underdose, overdose or accidental exposure to the active drug when adhesive squares remain on the liner after removal of the liner tabs or when adhesive squares remain on the skin after patch removal. Users also failed to follow the correct order for the liner tab removal which could expose a patient or caregiver to a large portion of the active drug before patch application. Therefore, we remain concerned that labeling enhancements will not adequately address the risks associated with the separation of (b) (4) the TDS (b) (4) if the inherent product design flaw is not resolved.

Based on the deficiencies noted with the study design, results and unvalidated labeling revisions we are unable to conclude that the Human Factors Labeling Comprehension Study confirms patients and caregivers understanding of how to safely and effectively apply, remove and dispose of the proposed ADLARITY patch.

[d] Corium Inc., Summary of Changes to IFU for Donepezil Transdermal Delivery System (TDA). NDA 212304. 2020 APR 10. Available from: \\cdsesub1\evsprod\nda212304\0014\m1\us\114-labeling\draft\labeling\11413-adlarity-label-changes-summary.pdf

5 DEFICIENCIES FOR DIVISION OF NEUROLOGY (DN1) TO COMMUNICATE TO CORIUM INC.

We refer to your Human Factors (HF) labeling comprehension study submitted to support your NDA 212304. We also refer to our January 31, 2020, comments stating that "labeling enhancements will not address the inherent product design flaw and the risk of the separation of [(b) (4)] the TDS [(b) (4)]" and that a labeling comprehension study (LCS) is not the appropriate mechanism to address the concerns. We note, however, that you conducted an LCS and we have reviewed the contents of that submission.

There are significant methodology concerns with your HF labeling comprehension study that raise concerns with interpretation of the study results. The patient user group did not include a representative sample size of 15 study participants, the simulation of patch application did not replicate real world use as patients and caregivers applied patches to an easel rather than the application areas described in the IFU, and based on your response to our IR for product samples, the intent-to-market patch was not used in the HF labeling comprehension study.

Moreover, the errors observed in this study indicate the labeling did not provide assurance that patients and caregivers could adequately identify adhesive squares that remained on the skin or on the liner. Therefore, we remain concerned that labeling enhancements alone will not minimize the risk to patients and caregivers if [(b) (4)] the transdermal system separates [(b) (4)].

Taking into consideration the totality of the information available to us at this time, including the deficiencies noted with the study design, study results, and unvalidated labeling revisions, we are unable to conclude that the Human Factors Labeling Comprehension Study confirms that the product labeling addresses the risks associated with the separation of [(b) (4)] the TDS [(b) (4)].

Appendix A:

A1. Link to labeling comprehension study submitted April 10, 2020:

\\cdsesub1\evsprod\nda212304\0014\m1\us\114-labeling\draft\comprehension-studies\labeling-comprehension-report.pdf

A2. Link to Summary of Changes to IFU submitted April 10, 2020:

\\cdsesub1\evsprod\nda212304\0014\m1\us\114-labeling\draft\labeling\11413-adlarity-label-changes-summary.pdf

A3: Response to Information Request for Sampled submitted May 1, 2020:

\\cdsesub1\evsprod\nda212304\0019\m1\us\12-cover-letters\cover-letter.pdf

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/s/

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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: 5/7/2020

TO: Division of Neurology Products
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212304

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

Celerion, Tempe: The Office of Regulatory Affairs (ORA) inspected the site in June 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: NDAs 212725 and 212726, and BLA 761045.

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observation:

- For BLA 761045, the firm did not possess the blinding codes from the end of the study through the inspection, therefore, the accuracy of the dosing with the blinded products could not be verified.

After review of the inspectional findings, OSIS recommended that the data from NDAs 212725 and 212726 be accepted for Agency review and that data from BLA 761045 be rejected (OSIS Final EIR Review-June 2019 inspection).

(b) (4): OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submission: BLA NON-RESPONSIVE.

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Celerion	2420 West Baseline Road, Tempe, AZ
Analytical	(b) (4)	

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LABEL, LABELING, AND PACKAGING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	April 16, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 212304
Product Name, Dosage Form, and Strength:	Adlarity (donepezil transdermal system), 5 mg/day and 10 mg/day
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Corium, Inc.
FDA Received Date:	September 30, 2019 and January 10, 2020
OSE RCM #:	2019-2155
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

This review responds to a request from the Division of Neurology 1 (DNP1) to review the proposed labels and labeling for Adlarity (donepezil transdermal system) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS & RECOMMENDATIONS

We identified areas of the label and labeling which should be revised to help ensure the safe use of the product. Section 3.1 and 3.2 below include the identified medication error issues, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

3.1 RECOMMENDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

A. Prescribing Information (PI)

1. Dosage and Administration Section

a. The dosing in the Highlights of the PI, does not state whether it represents the starting dose or the maintenance dose. The lack of clarity may contribute to wrong dose medication errors. We recommend clarifying whether the dosing in the Highlights refers to the starting dose or maintenance dose.

b. [redacted] (b) (4)

c. As currently presented in Section [redacted] (b) (4) 2.2 [redacted] (b) (4) (Switching to ADLARITY from Donepezil Tablets or Donepezil ODT), the time frame for increasing the dose may be misinterpreted. Consider revising '4-6 weeks' to read '4 to 6 weeks' in these sections and wherever else it appears.

2. How Supplied/Storage and Handling Section

   a. The NDC numbers are denoted by placeholders (i.e., XXXX-XXXX-XX) in Section 16 (How Supplied/Storage and Handling). Therefore, we are unable to assess the NDC numbers from a medication safety perspective. Replace the placeholders (i.e., XXXX-XXXX-XX) with the appropriate NDC number for both proposed strengths.

   b. The statement 'Used [redacted] (b) (4) should be folded with the adhesive surfaces pressed together and discarded [redacted] (b) (4), does not define what '[redacted] (b) (4)' means. Consider using the language in section 17 (Patient Counseling Information) of the PI to better instruct the prescriber regarding proper disposal – ' ...discard it out of the *reach and sight* of children and pets'. Alternatively, consider [redacted] (b) (4).

3.2 RECOMMENDATIONS FOR CORIUM, INC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Overpack Professional Sample; Container [Pouch] Labels and Carton Labeling; Trade and Professional Sample; 5 mg/hour and 10 mg/hour)

   1. The NDC numbers are denoted by a placeholder. Therefore, we are unable to assess the proposed NDC numbers from a medication safety perspective. Add the proposed NDC numbers to the labels and labeling for our review and comment.

   2. As currently presented on the labels and labeling, the product strength is not consistently expressed and may lead to misinterpretation. Ensure the strength is expressed as 'xx mg/day' wherever it appears on the labels and labeling to avoid confusion.

   3. The expiration date format is not defined on the container label and carton labeling. To minimize confusion and reduce the risk for deteriorated product medication errors, identify the format you intend to use. FDA recommends that

the human-readable expiration date on the product package label include a year, month, and non-zero day. Additionally, 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. If there are space limitations on the product package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. A hyphen or a space may be used to separate the portions of the expiration date.

4. The usual dosage statement is not present on the labels and labeling. The usual dosage statement is required per 21 CFR 201.55. We recommend you revise the container labels and carton labeling to read: Recommended dosage: See prescribing information and Instructions for Use for dosing and application instructions.

5. We note the product has heat exposure limitations. Specifically, the Prescribing Information (Section 2.4 and Section 17) states to avoid long exposure to external heat sources (e.g., excessive sunlight, saunas, solariums or heating pads). However, the container labels and carton labeling do not contain this warning. Add a statement, such as "Avoid applying heat" or a similar statement to the principal display panel of the labels and labeling.

6. The storage statement on the container labels and carton labeling is inconsistent with that presented in the Prescribing Information labeling. For increased comprehension by lay users, we recommend the storage statement be revised to read: "(b) (4)

7. We note the presence of a placeholder for the lot number and expiration date on the container labels and carton labeling. However, it is unclear how the lot number and expiration date will appear. Ensure that there are no other numbers located in close proximity to the lot number where it can be mistaken as the lot number[a] and ensure the lot number is clearly differentiated from the expiration date.[b]

8. The color scheme of the 10 mg/day strength statement (b) (4) and the proprietary name (Adlarity) appear in the same (b) (4) color ((b) (4)). The use of the same (b) (4) color font for the proprietary name and one of the product's strengths minimizes the difference between the two strengths, which may lead to wrong strength selection errors. Revise the font color of the

[a] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

[b] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

proprietary name or revise the color scheme of the 10 mg/day strength, so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.

9. The storage statement lacks instruction to store the patch in pouch until ready for use, which may lead to inappropriate storage. We recommend adding the instruction to "Keep ADLARITY in the individual sealed pouch until use" to the storage statement on the labels and labeling.

B. Container (Pouch) Labels (Trade and Professional Sample; 5 mg/day and 10 mg/day)

1. The 'rx only' statement appears more prominent than other important information on the PDP. Per our guidance, the proprietary name, established name, product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP[c]. Ensure the 'rx only' statement does not compete in prominence with the aforementioned critical information. Consider decreasing the font size and relocating the 'rx only' statement to the top or bottom of the PDP or address this concern by other means.
2. The strength statement appears twice on the principal display panel, which is unnecessary and clutters the label. Streamline the strength statement to appear once on the principal display panel as "xx mg/day".
3. The statement 'For Transdermal Use Only' is not prominent and may be overlooked, which may pose risk of wrong route of administration or wrong technique medication errors. Improve the prominence of the statement 'For Transdermal Use Only' to emphasize proper use of this product and to ensure it is not overlooked. To accomplish this, consider (b) (4) or address this concern by other means.
4. The net quantity statement (i.e., Contains 1 system) is located in close proximity to the product strength. From postmarketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel.

C. Carton Labeling (Trade and Professional Sample; 5 mg/day and 10 mg/day)

1. The patch disposal instructions on the carton labeling lack the important warning to dispose out of the reach of pets. We are concerned that this may result in inappropriate disposal, which could result in accidental exposure by pets. Revise

[c] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

the statement ' … [redacted]' to read '… [redacted]' wherever it appears in the disposal instructions (for example, on the back panel under [redacted]').

2. As presented, there is a 'flap' which appears in the lower right-hand corner of the principal display panel (PDP). The intent of this 'flap' is unclear (e.g., Is this a peel-off label to access additional product information or a graphic design?). Clarify the intent of this 'flap'.

3. As presented on the back panel, the [redacted] Delete this [redacted] from the carton labeling to avoid misinterpretation of this information.

4. The statement [redacted]' on the back panel of the carton labeling is inconsistent with the statement in the Prescribing Information (PI). Additionally, postmarketing reports suggest that negative statements may be misinterpreted as an affirmative action if the word "[redacted]" is overlooked. For consistency with the PI and to avoid misinterpretation, revise the statement ' [redacted]' to read 'Keep in the individually sealed pouch until use'.

D. Carton Labeling (Trade, 5 mg/day and 10 mg/day)

1. We note the presence of a [redacted] which overlaps the product strength ('XX mg') near the bottom of the principal display panel. We are concerned that users may misinterpret this [redacted] to mean that 4 systems are required for a XX mg dose. To avoid confusion, remove this [redacted] from the principal display panel, or address this concern by other means.

2. As currently presented, there is no placeholder for a product identifier on the carton labeling. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[d] The Act requires manufacturers and repackagers, respectively, 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 beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance. If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the human-readable and machine-readable (2-D data matrix barcode) product identifier to the carton labeling.

3. It is unclear whether pouches are intended for individual dispensing. The carton labeling contains important safety information that may not be available to users if pouches are dispensed individually. Clarify whether pouches are intended for

[d] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

individual dispensing or whether they should be dispensed in the sealed carton. If the latter, consider revising the carton labeling to state “Dispense in this sealed carton” on the principal display panel, or address this concern by other means.

E. Carton Labeling (Overpack, Professional Sample, 5 mg/day and 10 mg/day)

1. The readability of the net quantity statement can be improved. Consider revising the net quantity statement to read ‘Contains (b) (4) sample packs. Each sample pack contains one (b) (4) system’.

F. Instructions for Use (IFU)

1. (b) (4)

2. As currently presented in Step 1 ((b) (4)), the illustration identifying possible locations for the patch may be misinterpreted to mean that a patch should be applied to more than one site and could result in an overdose. We recommend you consider the labeling of other transdermal systems (e.g., Rivastigmine) as you determine how best to depict acceptable sites for patch application.

4 CONCLUSION

Our evaluation of the proposed Adlarity prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Section 3.1 for the Division and Section 3.2 for the Applicant. We advise that these recommendations be implemented prior to approval of this product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Adlarity received on September 30, 2019 from Corium, Inc.

Table 2. Relevant Product Information for Adlarity	
Initial Approval Date	N/A
Active Ingredient	donepezil
Indication	Mild, moderate and severe Alzheimer's disease
Route of Administration	transdermal
Dosage Form	Transdermal system
Strength	5 mg/day and 10 mg/day
Dose and Frequency	(b) (4)
How Supplied	One carton contains 4 patches individually packaged in sealed pouches
Storage	(b) (4) Keep patch in the pouch until use. Used (b) (4) should be folded with the adhesive surfaces pressed together and discarded (b) (4) .
Container Closure	(b) (4) pouch (b) (4) .

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 16, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, ‘Adlarity’ and ‘donepezil’. Our search identified no previous reviews relevant to this one.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

- Patch label received on September 30, 2019
- Container (pouch) label received on September 30, 2019
- Carton labeling received on September 30, 2019
- Professional Sample container (pouch) label received on September 30, 2019
- Professional Sample Carton Labeling received on September 30, 2019
- Instructions for Use received on January 10, 2020, available from \\cdsesub1\evsprod\nda212304\0006\m1\us\114-labeling\draft\labeling\11413-draft-text-labeling.pdf
- Prescribing Information (Image not shown) received on January 10, 2020, available from \\cdsesub1\evsprod\nda212304\0006\m1\us\114-labeling\draft\labeling\11413-draft-text-labeling.pdf

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

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