CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212304Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 212304
Review #2

Drug Product Name	ADLARITY (donepezil transdermal system)
Dosage Form	Transdermal system
Strength	5 mg/day, 10 mg/day
Route of Administration	Transdermal
Rx/OTC Dispensed	Rx
Applicant	Corium Inc.
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	Andrei Ponta	Martha Heimann
Manufacturing	Youmin Wang	Yubing Tang
Microbiology	N/A	N/A
Biopharmaceutics	Kaushalkumar Dave	Ta-Chen Wu
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Caroline Strasinger/Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submission(s)	Document Date	Discipline(s) Affected
SD-028, NDA Resubmission	9/1/3021	Drug product, biopharmaceutics, manufacturing
SD-030, Quality Response to Information Request (QRIR)	11/2/2021	Drug product

Submission(s)	Document Date	Discipline(s) Affected
SD-031, Quality Information	12/20/2021	Drug product
SD-033, QRIR	1/24/2022	Drug product, biopharmaceutics
SD-034, QRIR	1/27/2022	Drug product
SD-035, QRIR	1/27/2022	Drug product, manufacturing

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II		(b) (4)	Adequate	May 19, 2020	
	IV			N/A[1]	N/A[1]	
	IV			N/A[1]	N/A[1]	
	III			N/A[1]	N/A[1]	
	IV			N/A[1]	N/A[1]	
	III			N/A[1]	N/A[1]	
	III			N/A[1]	N/A[1]	
	III			N/A[1]	N/A[1]	

[1] Adequate information provided in NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
IND	129778	Development of Adlarity (donepezil) transdermal system for treatment of mild, moderate, and severe Alzheimer's Disease
NDA	(b) (4)	Aricept (donepezil) tablets. Reference under 505(b) to support safety and efficacy of donepezil

2. CONSULTS

N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 212304 for Adlarity (donepezil) transdermal system (TDS) is recommended for **APPROVAL** from a product quality perspective. In the NDA resubmission, the applicant adequately addressed the outstanding quality deficiencies communicated in the 7/23/2020 Complete Response Letter (CRL).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed Donepezil TDS is a matrix-type TDS comprised of six layers, including an incorporated overlay, an active drug matrix layer, a (b) (4) membrane, a contact adhesive, and a release liner. Two strengths are proposed that will deliver 5 mg or 10 mg donepezil per day over a seven-day period. Total drug content is 96.9 mg donepezil for the 5 mg/day strength and 193.7 mg for the 10 mg/day strength. (b) (4), the active delivery area (b) (4) is segmented into four and nine segments for the 5 mg/day and 10 mg/day strengths, respectively. Segmenting the TDSs is intended to (b) (4) during the 7-day wear period.

(b) (4)

The active pharmaceutical ingredient (API) used to manufacture the Donepezil TDS is donepezil HCl [redacted (b) (4)].

Proposed indication(s) including intended patient population	For the treatment of dementia of Alzheimer's type in patients with mild, moderate, and severe Alzheimer's Disease.
Duration of treatment	Chronic. Applied once weekly for seven-day wear.
Maximum daily dose	10 mg/day
Alternative methods of administration	None

B. Quality Assessment Overview

NDA 212304 was originally submitted on 9/13/2019. During the review of the original NDA submission, the Office of Product Quality (OPQ) team identified major product quality issues related to the design of the TDS and delamination, drug product controls, product stability, and changes in the manufacturing process between the product used for clinical studies and the final to-be-marketed (TBM) product. The original NDA submission was recommended for a Complete Response from a product quality perspective and the CRL was issued on 7/23/2020. Refer to the 6/20/2020 OPQ Integrated Quality Review[1] for further details.

As discussed below, the 9/1/2021 NDA resubmission, and the applicant's subsequent responses to information requests, addressed all outstanding product quality concerns.

Drug Substance: Adequate First Cycle

In the original NDA, the applicant proposed two suppliers for donepezil hydrochloride bulk drug substance (DS), i.e., [redacted (b) (4)] and [redacted (b) (4)]. [redacted (b) (4)] was withdrawn as a drug substance supplier in the resubmission. There are no other changes, and no new information was submitted.

[1] (https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8057259d&showAsPdf=true)

Drug Product: Adequate

Key Issues from First Cycle:

Delamination

(b) (4)

Furthermore, the applicant has added a test to confirm that the individual segments cannot be removed from the overlay. This test is designed to address the concern with the ease of separation (b) (4). Release and stability data from (b) (4) batches confirm that (b) (4) cannot be removed (b) (4).

Changes During Long-Term Storage

During the original review, there was an overarching concern that the drug product on release was not equivalent to the drug product after long-term storage. Multiple changes were observed during long-term stability studies:

(b) (4)

In addition to these differences, a significant drop in in vitro drug release results was observed.

As part of the resubmission, (b) (4) the applicant provided data demonstrating that product stored under refrigerated conditions meets all the proposed specifications. Furthermore, changes in excipient and assay content have not been observed to date, when the drug product is stored under refrigerated conditions. Specifically, (b) (4) content remains constant during long-term storage (refrigerated conditions). Similarly, assay remains relatively constant throughout long-term storage. The applicant has also provided data showing that refrigerated storage (b) (4). In vitro drug release results trend slightly downward when the drug product is stored under refrigerated conditions; however, the results remain within the proposed limits.

As discussed below under *Biopharmaceutics,* the applicant has also conducted a Phase 1 PK study (Study CL-P-20004), to evaluate the bioequivalence of (b) (4) Adlarity TDS stored under refrigerated conditions for approximately 24 months (i.e., near the end of the proposed shelf life) to the to-be-marketed, (b) (4) Adlarity TDS stored under refrigerated conditions for approximately 5 months (i.e., near the beginning of the proposed shelf life).

Additional Issues from First Cycle:

Addition of (b) (4)

As part of the amendment dated 4/10/2020, the applicant updated the release liner (b) (4). No data has been provided to demonstrate that the (b) (4) is robust (b) (4) and remains unchanged during storage ((b) (4)). Furthermore, the applicant did not provide any release or stability results for drug product manufactured with the newly proposed release liner. In the NDA resubmission, the applicant indicated that the release liner for the commercial batches is a blue-tinted liner with no (b) (4), as in the original NDA submission. The (b) (4) has been removed from the liner; thus, this issue has been resolved.

Pouch Seal Strength

The applicant was asked to update the pouch seal strength acceptance criteria based on all available release and stability data for the primary registration batches and has done so.

Crystal Inspection

The applicant provided the requested details regarding the crystal inspection. This included the method used to [redacted] (b) (4)

Outstanding Information Requests

The applicant committed to addressing a number of information requests from the las review cycle. The applicant provided adequate responses for each of the information requests (developing a method for separation strength of [redacted] (b) (4), providing a comparison of donepezil free base and donepezil HCl content in the clinical drug product batches, and providing in-use photostability results).

Shelf Life

Due to the numerous concerns identified during the first cycle, no shelf life could be assigned. In the resubmission, the applicant provided 12 months of long-term data (2°C - 8°C) and 6 months of accelerated data (25°C ± 2°C/60% RH ± 5% RH) for [redacted] (b) (4) batches manufactured by the final commercial process. Based on the data, a **24-month expiration dating period** is assigned for the product when **stored at 2°C - 8°C**.

Labeling: Adequate

The proposed labeling is generally adequate; however, concerns regarding the identity of the active ingredient and communicating that both donepezil HCl and donepezil are present in the finished product, with amounts of both listed in labeling, were identified. The draft prescribing information submitted simply stated in Section 16 Description that "[redacted] (b) (4)" The proposed container labels correctly list the amount of drug delivered (5 mg/day or 10 mg/day) as the primary expression of strength. However, the container labels list [redacted] (b) (4) " The latter statement is not accurate as: a) [redacted] (b) (4); and b) donepezil base, not the salt, is the form released from the system. The FD&C Act requires name(s) and amount(s) of active ingredient(s). However, at drug product release, the amounts of donepezil HCl and donepezil base present may range between 65% to 85% and 15% to 35%, respectively. To ensure that labeling should reflects the design of the finished DP in that it contains both base and salt and [redacted] (b) (4)

(b) (4), it is recommended that labeling state the equivalent total amount of donepezil base (active moiety) along with the range of amounts of both donepezil HCl and donepezil base, e.g., for carton container:

- "Each system delivers donepezil 10 mg/day. Each system contains 176.7 donepezil (present as donepezil (15% to 35%) and donepezil HCl (65% to 85%))."
- "Each system delivers donepezil 5 mg/day. Each system contains 88.4 mg donepezil (present as donepezil (15% to 35%) and donepezil HCl (65% to 85%))."

Similar language will be use in Section 16 of the prescribing information. The OPQ Product Quality Labeling Committee (PQLC) was consulted for labeling statements related to the presence of salt and base forms discussed above. The recommendation has been communicated to, and accepted by, the applicant.

Manufacturing: Adequate

Key Issues from First Cycle:

Delamination:

(b) (4)

Manufacturing Process Changes

The first cycle review identified multiple process changes that were made between the pivotal bioequivalence batch the to-be-marketed products. However, the Biopharmaceutics reviewer determined that the applicant's in vitro bridging strategy was inadequate. As discussed below under *Biopharmaceutics,* the applicant has conducted a new Phase 1 PK study (Study CL-P-20003) that compared the (b) (4) TBM product to the Listed Drug, Aricept (donepezil HCl) tablets.

(b) (4)

(b) (4)
, the applicant did not propose any controls on base content in the laminate. Further, it was unclear what percent of donepezil was present *as the base* in clinical, registration, and the proposed commercial batches. The applicant did commit to developing a test; however, the information could not be reviewed during the firsts cycle due to the lateness of the submission. The test was reviewed as part of the resubmission and is deemed adequate.

Facilities

The status of a critical DS intermediate site for (b) (4)-supplied DS was Official Action Indicated (OAI) as of (b) (4). Additionally, a different testing site was submitted in an unsolicited amendment on 04/28/2020 and was not reviewed during the first cycle. Therefore, a withhold was recommended.

As (b) (4) was withdrawn as a DS supplier in the resubmission, the OAI DS intermediate site was withdrawn. All facilities currently proposed for or manufacture or testing of Donepezil HCl and Adlarity (donepezil transdermal are adequate. Facility status should be verified prior to final action.

Biopharmaceutics: Adequate

Key Issues from First Cycle:

In Vitro Release

The proposed in vitro drug release testing (IVRT) method and acceptance criteria were deemed adequate during the first cycle; however, the applicant was advised that this would be reassessed if changes were made to the system or manufacturing process. The IVRT results provided in the resubmission for (b) (4) drug product used in BA/BE studies CL-P-20003 and CL-P-20004 were evaluated to verify the applicant's claim that (b) (4) is not expected to alter the drug release behavior of the proposed drug product. Similarity factor (f2) analysis comparing the clinical and registration batches used in the original submission and (b) (4) batches in the current submission indicates that there is no significant difference in the IVRT profiles of these batches. Since the drug product used in the original submission and in the current submission are not significantly different, except for the (b) (4), and the IVRT profiles of these products are found to be similar, the IVRT method remains adequate.

Based on the full-profile IVRT data of the clinical and registration batches submitted under the current submission, the applicant's originally proposed IVRT acceptance

criteria were found to be permissive. The Agency recommended, and the applicant has agreed to, the following IVRT acceptance criteria for quality control testing:

1 Hour: (b) (4)%
8 Hours: (b) (4)%
24 Hours: (b) (4)%
48 Hours: (b) (4)%
168 Hours: NLT (b) (4)%

Formulation Bridging

During the first cycle, it was determined that due to significant manufacturing process changes between the bioequivalence batch and the original TBM product, differences in the in vitro release test methods used, and absence of other key information (e.g., base content), a bioequivalence study would be needed to bridge the clinical and TBM products. The applicant was advised to conduct a new bioequivalence study of the final TBM product versus the listed drug, Aricept (donepezil) tablets. To resolve this deficiency, and establish a bridge between the new, (b) (4) TDS and the listed drug, the Applicant conducted a Phase 1 PK study (Study CL-P-20003) with (b) (4) TDS manufactured using the proposed commercial process versus Aricept. The Clinical Pharmacology Reviewer, Dr. Min Li, confirmed that the study established bioequivalence of the (b) (4) TDS with Aricept.

(b) (4)

Shelf Life

To address the concerns regarding changes over the shelf-life of the TDS, the applicant (b) (4) and conducted a Phase 1 pharmacokinetic (PK) study (CL-P-20004) comparing recently manufactured (b) (4) TDS (approximately 5 months from date of manufacture) to older (b) (4) TDS (approximately 24 months from date of manufacture), with both sets of patches stored under

refrigerated conditions. The Clinical Pharmacology Reviewer, Dr. Min Li, confirmed that Study CL-P-20004 is acceptable from a Clinical Pharmacology perspective.

APPEARS THIS WAY ON ORIGINAL

FDA-approved IVRT method and acceptance criteria for the proposed ADLARITY™ (donepezil) transdermal system, 5 mg/day equivalent and 10 mg/day equivalent:

Apparatus	USP Apparatus 5 (Paddle over Disk) with Transdermal System Holding Wire Screen (TSHWS)
Paddle Speed	100 rpm
Volume	900 mL
Medium	0.02 M Sodium Acetate Buffer, pH 4.5
Temperature	32.0 ± 0.5˚C
Acceptance Criteria	1 Hour: (b) (4) % 8 Hours: (b) (4) % 24 Hours: (b) (4) % 48 Hours: (b) (4) % 168 Hours: NLT (b) (4) %

Environmental: Adequate First Cycle

C. Risk Assessment

The first cycle risk assessment is repeated below, followed by the final risk assessment. The final risk assessment only covers attributes/CQAs that were not adequately mitigated during the first cycle review.

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Donepezil Assay/Related Substance	Formulation, raw materials, container closure, process, scale, equipment	L	(b) (4)	L	Assay does not differentiate between salt and base
(b) (4) Base Assay	Formulation ((b) (4) , stability, (b) (4)	H		H	No Acceptance Criterion has been established
Lauryl Lactate (LL) Content	Formulation, stability, (b) (4)	M		H	(b) (4)
Sorbitan Monolaurate (SM), Triethyl Citrate (TC) Content (Tests are not currently included)	Formulation, stability, (b) (4)	M		H	(b) (4)

Cold Flow (active area, border, pouch transfer)	Formulation, raw materials, stability	L	(b) (4)	L	Relatively little cold flow of border observed on stability; some active area is notable (b) (4)
Adhesion (contact adhesive, border adhesive)	Formulation, raw materials, process, stability	M		L	(b) (4)
Release Liner Removal (contact adhesive, border adhesive)					
Probe Tack (contact adhesive, border adhesive)					
Dynamic Shear					
Separation Strength (Test not currently included)	Formulation, manufacturing process, stability	H		H	The applicant has not established a method or criteria; The applicant must first fix the inherent separation issue and then establish new criteria in next review cycle
Crystals	Formulation, (b) (4), (b) (4), (b) (4), stability,	L		L	(b) (4)

IVRT	Formulation; stability; (b) (4)	L	(b) (4)	M	The 24-hour time point has a decrease of (b) (4)% over 24 months; 48-hour time a decrease of (b) (4)%; 168-hour time point has a decrease of (b) (4) % Largest drop appears to occur during the first 6 months of storage; though slower decrease is observed afterwards, it is important to note that the decrease across all three time points continues.

Final Risk Evaluation

From Initial Risk Identification			Review Assessment		
Attribute / CQA	**Factors that can impact the CQA**	**1st Cycle Evaluation**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
(b) (4) base assay	Formulation (b) (4) stability, (b) (4)	H	(b) (4)	L	
Lauryl lactate content	Formulation, stability, (b) (4)	H		L	
Sorbitan monolaurate and triethyl citrate content	Formulation, stability, (b) (4)	H		L	

From Initial Risk Identification			Review Assessment		
Attribute / CQA	**Factors that can impact the CQA**	**1st Cycle Evaluation**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Separation strength	Formulation, manufacturing process, stability	**H**	(b) (4)	**L**	
IVRT	Formulation; stability; (b) (4)	**M**		**L**	

D. List of Deficiencies for Complete Response

Not Applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
Senior Product Quality Assessor for Neurology Products
Office of New Drug Products

3/3/2022

NDA 212304

Appendix to Executive Summary

OPPQ/PQL Labeling recommendations for
ADLARITY (donepezil transdermal system)

Martha Heimann

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

(b) (4)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	ADLARITY (donepezil transdermal system)
Dosage form, route of administration	Transdermal system, transdermal
Controlled drug substance symbol	Not Applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	System 5 mg/day and 10 mg/day

Is the information accurate? ☒ Yes ☐ No

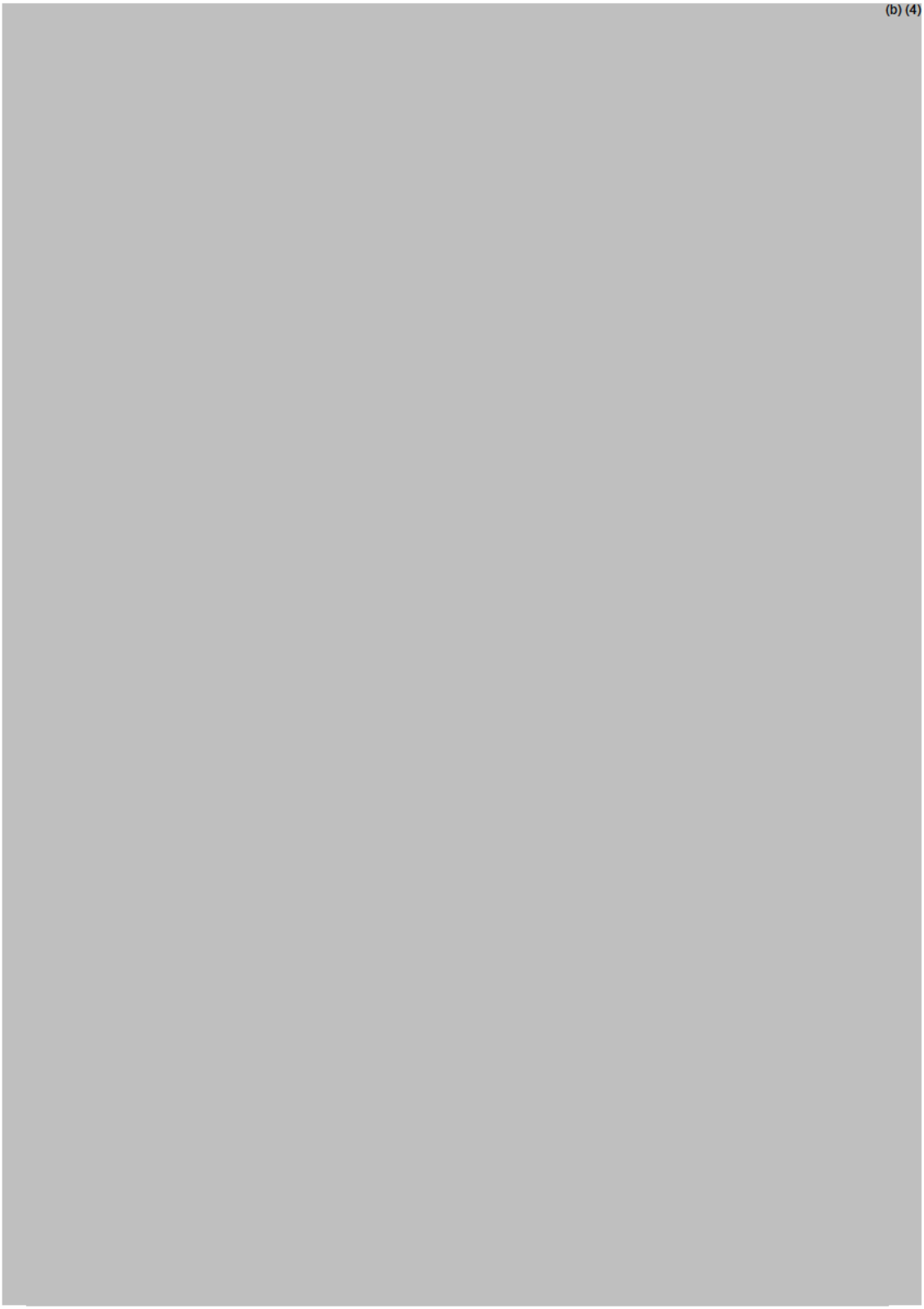
The Applicant includes (b) (4) in the dosage forms and strength section and will be asked to remove them.

The Applicant will be asked to replace the term "(b) (4)" with "system.

2. *Section 2 Dosage and Administration*

(b) (4)

(b) (4)



Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	

Special instructions for product preparation	Conforms

Is the information accurate? ☒ Yes ☐ No

3. *Section 3 Dosage Forms and Strengths*

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	5 mg/day 10 mg/day
Strengths: in metric system	Transdermal system: 5 mg/day 10 mg/day
Active moiety expression of strength with equivalence statement	Equivalency statement not present; however, strength is donepezil delivered / day.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Tan colored rectangular TDS with rounded corners

Is the information accurate? ☒ Yes ☐ No

4. *Section 11 Description*

(b) (4)

(b) (4)

[redacted]

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	ADLARITY (donepezil transdermal system) Reviewer's Note: Applicant will be asked to include established name.
Dosage form and route of administration	Transdermal: 5 mg/day; 10 mg/day
Active moiety expression of strength with equivalence statement (if applicable)	Equivalency statement not present; however, strength is donepezil delivered / day.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Acrylate polymer, crospovidone, glycerol, lauryl lactate, sorbitan monolaurate, sodium bicarbonate, triethyl citrate Reviewer's Note: • Applicant will be asked to remove microporous adjective from the membrane • Applicant will be asked to include crospovidone [redacted] (b) (4) • Applicant will be asked to include ascorbyl palmitate and polypropylene membrane.
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Present
Chemical name, structural formula, molecular weight	Present
If radioactive, statement of important nuclear characteristics.	Not Applicable

Other important chemical or physical properties (such as pKa or pH)	Not Applicable

Is the information accurate? ☒ Yes ☐ No

The Applicant will be asked to replace the term "(b) (4)" with "system. The size of the systems is not included Additional corrections have been identified in the table and will be communicated to the Applicant.

5. ***Section 16 How Supplied/Storage and Handling***

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Transdermal: 5 mg/day 10 mg/day
Available units (e.g., bottles of 100 tablets)	Carton of four
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Present
Special handling	Do not freeze Keep in pouch until use
Storage conditions	Refrigerated
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Present

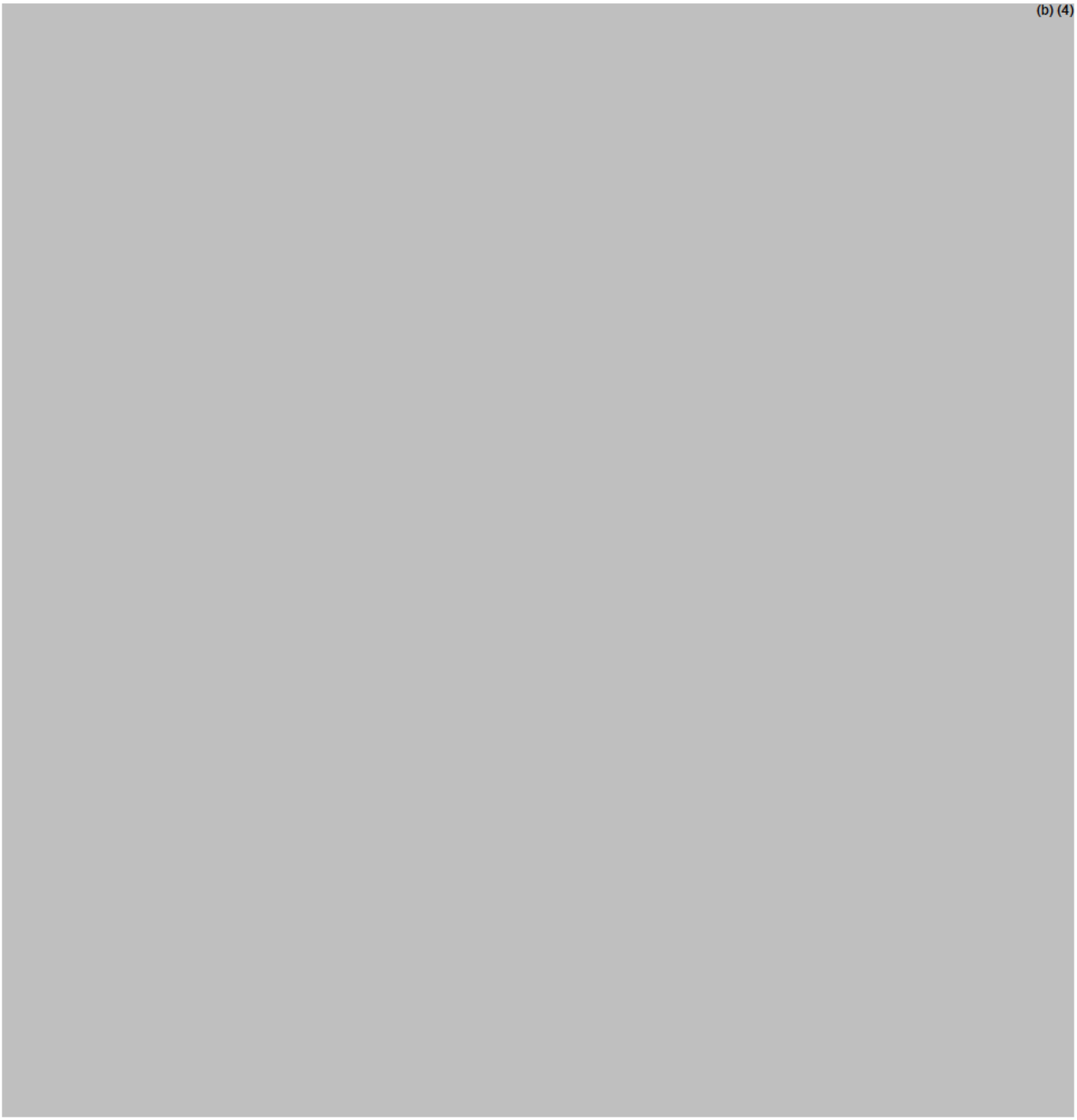
Reviewer's Assessment of Package Insert: *Adequate*

Prescribing Information complies with all regulatory requirements from a CMC perspective.

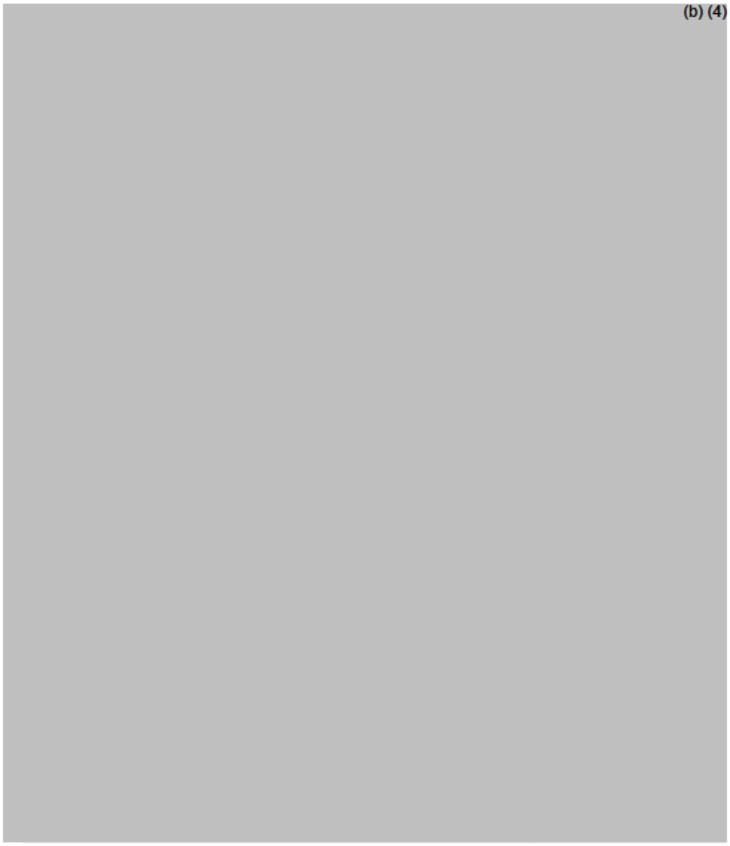
However, some revisions have been identified and will be communicated to the Applicant as part of DNP labeling negotiations.

II. Labels:

(b) (4)



3. ***Backing Layer***



Item	Information provided in the pouch label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ADLARITY (donepezil transdermal system) Reviewer's Note: Applicant will be asked to remove "(b) (4)" from all labeling (including carton container)	ADLARITY (donepezil transdermal system) Reviewer's Note: Applicant will be asked to remove "(b) (4)" from all labeling (including carton container)
Dosage strength	5 mg / day 10 mg / day	5 mg / day 10 mg / day
Net contents	Complies	Complies
"Rx only" displayed prominently on the main panel	Complies	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies	Complies
Lot number and expiration date (21 CFR 201.17)	Complies	Complies
Storage conditions	Complies	Complies
Bar code (21CFR 201.25)	Complies	Complies
Name of manufacturer/distributor	Complies	Complies
And others, if space is available	Not Applicable	

Reviewer's Assessment of Labels: *Adequate Pending Updates During Labeling Negotiations.*

The container labels comply with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, name of manufacturer, net contents, strength, and the name (proprietary and established).

However, the term (b) (4) is used in the container/closure label where system should be used. This will be communicated to the Applicant as part of DNP labeling negotiations.

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date: Andrei Ponta

Andrei Ponta

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Martha Heimann

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BIOPHARMACEUTICS

Application No: NDA-212304-ORIG-1-RESUB-28; 505(b)(2)
Drug Product Name/Strengths: ADLARITY™ (Donepezil HCl) Transdermal System; 5 mg/day equivalent, 10 mg/day equivalent
Route of Administration: Transdermal
Indication: Treatment of Dementia of the Alzheimer's Type
Applicant Name: Corium, Inc.
Date of Submission: 09/30/2019 (Original Submission); 09/13/2021 (Resubmission)
Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Ta-Chen Wu, PhD

RECOMMENDATION: ADEQUATE

INTRODUCTION

The original submission for NDA 212304 was submitted to the FDA on 09/30/2019. However, due to concerns related to drug product quality and bridging between the drug product batches used in the pivotal study P-15086 and the to-be-marketed drug product, the Agency issued a Complete Response (CR) Letter on 07/23/2020[1] and included the following Biopharmaceutics deficiency in the CR Letter:

(b) (4)

Applicant's Responses to the CR Letter:

With the resubmission, the Applicant provided responses to address the deficiencies/concerns detailed in the CR Letter, as summarized below:

1. To address the concerns of TDS adhesion, the Applicant modified the drug product manufacturing process to include (b) (4) of the TDS.
2. To address the concerns regarding the shelf-life of the TDS, the Applicant (b) (4). The Applicant also conducted a Phase 1 pharmacokinetic (PK) study (CL-P-20004) comparing recently manufactured (b) (4) TDS (approximately 5 months from date of manufacture) to older (b) (4)

[1] \\CDSESUB1\evsprod\nda212304\0026\m1\us\16-meetings\fda-letter-07232020-complete-response-darrts.pdf

TDS (approximately 24 months from date of manufacture), with both sets of patches stored under refrigerated conditions.

3. To establish a bridge between the new, (b) (4) TDS and the listed drug, the Applicant conducted a Phase 1 PK study (Study CL-P-20003) with (b) (4) TDS manufactured using the proposed commercial process.

Note that the Clinical Pharmacology Reviewer, Dr. Min Li, confirmed that Study CL-P-20004 is acceptable from a Clinical Pharmacology perspective. In addition, Dr. Li confirmed that Study CL-P-20003 establishes bioequivalence between the to-be-marketed (b) (4) TDS [for both the 5 mg/day (dose-normalized) and 10 mg/day strengths] and between 10 mg/day oral Aricept® (LD) and both the 5 mg/day (dose-normalized) and 10 mg/day strengths of the (b) (4) TDS.

BIOPHARMACEUTICS REVIEW

IVRT Method

The newly proposed (b) (4) drug product used in the studies CL-P-20003 and CL-P-20004 is similar to the drug product used in the original submission except for the (b) (4). The (b) (4) is not expected to alter the drug release behavior of the proposed drug product. To verify the Applicant's claim, this Reviewer compared the IVRT profiles (***Appendix 1***) and performed similarity factor (f2) analysis comparing the clinical and registration batches used in the original submission and in the current submission. The similarity factor analysis (***Appendix 1***) indicates that there is no significant difference in the IVRT profiles of these batches. Since the drug product used in the original submission and in the current submission are not significantly different, except for the (b) (4), and the IVRT profiles of these products are found to be similar, the IVRT method proposed by the Applicant (***see Conclusion and Recommendation***), previously reviewed and deemed adequate by this Reviewer[2] under the original submission, remains adequate and is applicable to the newly proposed (b) (4) drug product under the current submission.

IVRT Acceptance Criteria

Based on the full-profile IVRT data of the clinical and registration batches submitted under the current submission, the Applicant's originally proposed IVRT acceptance criteria were found to be permissive. The Agency recommended the Applicant to implement the following IVRT acceptance criteria for QC testing of the proposed drug product (IR dated 01/19/2022):

1 Hour: (b) (4)%
8 Hours: (b) (4)%
24 Hours: (b) (4)%
48 Hours: (b) (4)%
168 Hours: NLT (b) (4)%

In response (dated 01/24/2022[3]), the Applicant accepted the FDA recommendation and revised the acceptance criteria accordingly[4].

[2] https://panorama fda.gov/task/view?ID=5df261040011402fce7ff4b0ef9322bd
[3] \\CDSESUB1\evsprod\nda212304\0033\m1\us\111-information-amendment\ir-response.pdf
[4] \\CDSESUB1\evsprod\nda212304\0034\m3\32-body-data\32p-drug-prod\corplex-donepezil-tds\32p5-contr-drug-prod\32p51-spec\32p51-specifications.pdf

Formulation Bridging

The drug product used in the clinical studies CL-P-20003 and CL-P-20004 is same as the to-be-marketed drug product. Therefore, no bridging studies are required for the proposed drug product.

(b) (4)

Conclusion and Recommendation:

From a Biopharmaceutics perspective, NDA 212304 for the proposed ADLARITY™ (donepezil HCl) Transdermal System, 5 mg/day equivalent and 10 mg/day equivalent, is deemed adequate and recommended for approval. The following IVRT method and acceptance criteria are approved for QC testing of the proposed drug product at batch release and on stability:

FDA-approved IVRT method and acceptance criteria for the proposed ADLARITY™ (Donepezil HCl) Transdermal System, 5 mg/day equivalent and 10 mg/day equivalent:

Apparatus	USP Apparatus 5 (Paddle over Disk) with Transdermal System Holding Wire Screen (TSHWS)
Paddle Speed	100 rpm
Volume	900 mL
Medium	0.02 M Sodium Acetate Buffer, pH 4.5
Temperature	32.0 ± 0.5°C
Acceptance Criteria	1 Hour: (b) (4)% 8 Hours: (b) (4)% 24 Hours: (b) (4)% 48 Hours: (b) (4)% 168 Hours: NLT (b) (4)%

Appendix 1

Figure 1. Comparative mean IVRT profiles of clinical and registration batches of the original submission and the current submission

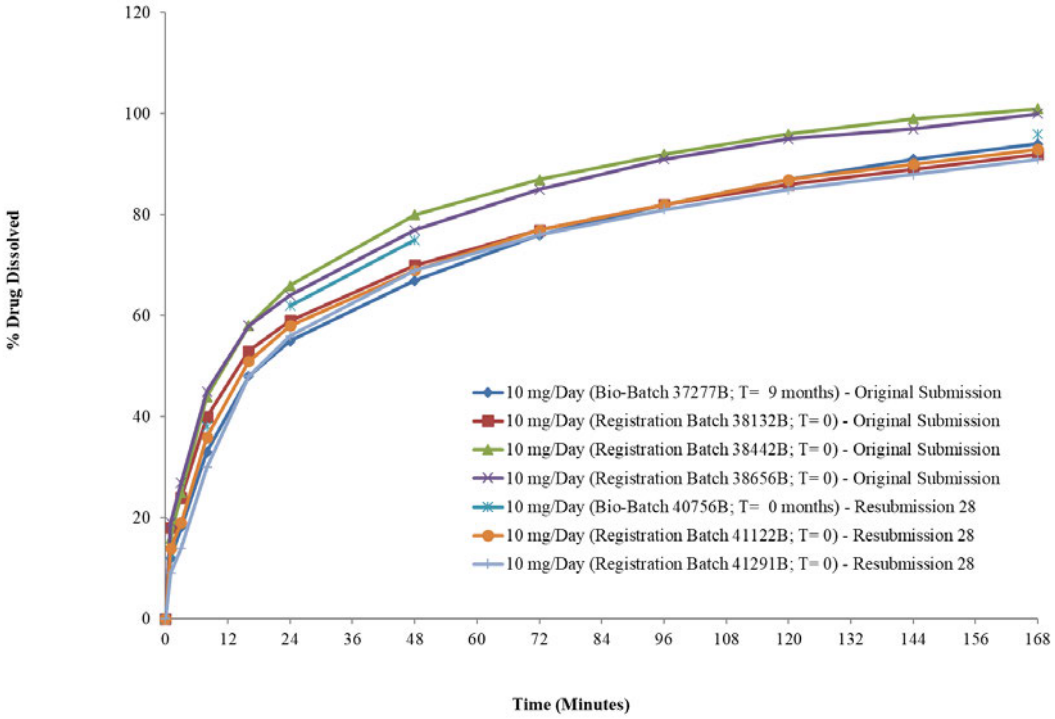


Table 1. Comparative mean IVRT profiles of clinical and registration batches of the original submission and the current submission

Time (Hrs)	10 mg/Day (Bio-Batch 37277B; T= 9 months) - Original Submission	10 mg/Day (Registration Batch 38132B; T= 0) - Original Submission	10 mg/Day (Registration Batch 38442B; T= 0) - Original Submission	10 mg/Day (Registration Batch 38656B; T= 0) - Original Submission	10 mg/Day (Bio-Batch 40756B; T= 0 months) - Resubmission 28	10 mg/Day (Registration Batch 41122B; T= 0) - Resubmission 28	10 mg/Day (Registration Batch 41291B; T= 0) - Resubmission 28
0	0	0	0	0	0	0	0
1	12	18	16	19	13	14	9
3	18	24	25	27	NA	19	14
8	33	40	44	45	38	36	30
16	48	53	58	58	NA	51	48
24	55	59	66	64	62	58	56
48	67	70	80	77	75	69	69
72	76	77	87	85	NA	77	76
96	82	82	92	91	NA	82	81
120	87	86	96	95	NA	87	85
144	91	89	99	97	NA	90	88
168	94	92	101	100	96	93	91

NA= Not available

Table 2. Similarity factor (f2) analysis for batches shown in Figure 1

Bio-Batch from Resubmission 28		**Bio-Batch and Registration Batches from Original Submission**	**Similarity Factor (f2) Calculated by this Reviewer**
10 mg/Day (Bio-Batch 40756B; T= 0 months) - Resubmission 28	Versus	10 mg/Day (Bio-Batch 37277B; T= 9 months) - Original Submission	65.12
10 mg/Day (Bio-Batch 40756B; T= 0 months) - Resubmission 28	Versus	10 mg/Day (Registration Batch 38132B; T= 0) - Original Submission	71.22
10 mg/Day (Bio-Batch 40756B; T= 0 months) - Resubmission 28	Versus	10 mg/Day (Registration Batch 38442B; T= 0) - Original Submission	67.75
10 mg/Day (Bio-Batch 40756B; T= 0 months) - Resubmission 28	Versus	10 mg/Day (Registration Batch 38656B; T= 0) - Original Submission	67.94

Kaushalkumar Dave

Digitally signed by Kaushalkumar Dave
Date: 2/03/2022 10:32:07PM
GUID: 5575db68006e2262805f2e6449c54250

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 2/03/2022 10:35:10PM
GUID: 508da6df000269e151ff37cd8f4e13a1

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTHA R HEIMANN
03/03/2022 01:26:34 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 212304
Assessment #1

Drug Product Name	ADLARITY (donepezil transdermal system)
Dosage Form	Transdermal system
Strength	5 mg/day, 10 mg/day
Route of Administration	Transdermal
Rx/OTC Dispensed	Rx
Applicant	Corium Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (0001)	30-SEP-2019	OPQ
Quality Response to IR (0002)	24-OCT-2019	OPQ (Samples Provided)
Quality Response to IR (0004)	20-DEC-2019	DP/OPMA (Response to 20-NOV-2020 Skype Call)
Subcategories - Quality Response to IR (0006)	10-JAN-2020	DP/Labeling/DMEPA
Quality Response to IR (0007)	10-JAN-2020	DP/Biopharm/OPMA/Adhesion Consult
Quality Response to IR (0008)	31-JAN-2020	DP/OPMA
Quality Response to IR (0009)	7-FEB-2020	DP/Biopharm
Quality Response to IR (0010)	28-FEB-2020	DP
Quality Response to IR (0012)	31-MAR-2020	DP/Biopharm/OPMA
Quality Response to IR (0013)	31-MAR-2020	DP
Subcategories - Quality Response to IR (0014)	10-APR-2020	DP/Labeling/DMEPA
General Correspondence (0015)	17-APR-2020	OPQ/Request for Teleconference (meeting package)
Quality Response to IR (0016)	17-APR-2020	DP/"clinical" layer separation

The below submissions were NOT assessed in this review cycle

Submission(s)	Document Date	Discipline(s) Affected
Quality Response to IR (0017)	28-APR-2020	OPMA/Biopharm
Quality Response to IR (0020)	22-MAY-2020	DP
Quality Response to IR (0022)	15-JUN-2020	DP/OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rajan Pragani	Suong Chen
Drug Product	Andrei Ponta	Julia Pinto
Manufacturing	James Norman	Yubing Tang
Microbiology	N/A	
Biopharmaceutics	Kaushalkumar Dave	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Walters/Bamidele (Florence) Aisida	
Application Technical Lead	Caroline Strasinger	
Biostats/Adhesion	Chao Wang	Meiyu Shen
Adhesion	Caroline Strasinger	N/A
Environmental	Andrei Ponta	Julia Pinto

RELATED/SUPPORTING DOCUMENTS

A. **DMFs:**

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II		(b) (4)	Adequate	June 10, 2020	LOA: Apr 16, 2018
	II			Adequate	May 19, 2020	LOA: Jun 28, 2016
	IV			N/A[1]	N/A[1]	LOA: Aug 12, 2016
	IV			N/A[1]	N/A[1]	LOA: Nov 8, 2018
	III			N/A[1]	N/A[1]	LOA: July 7, 2016
	IV			N/A[1]	N/A[1]	LOA: Nov 29, 2016
	III			N/A[1]	N/A[1]	LOA: Jun 30, 2019
	III			N/A[1]	N/A[1]	LOA: Oct 5, 2007
	III			N/A[1]	N/A[1]	LOA: Jun 24, 2009

[1] Adequate information provided in NDA.

B. **Other Documents:** *IND, RLD, or sister applications*

Document	Application Number	Description
IND	129778	Corplex (Donepezil) transdermal system for treatment of mild, moderate, and severe Alzheimer's Disease from Corium International Inc. Active since 18-OCT-2016.

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has **not** provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The OPQ review team recommends that a **Complete Response (CR)** be issued for NDA 212304, ADLARITY (donepezil transdermal system). Significant drug product and manufacturing deficiencies were communicated in a Discipline Review Letter (DRL) dated May 4, 2020. An email communication dated May 29, 2020 further clarified the points of the DRL to the Applicant.

The deficiencies identified in the DRL precluded labeling discussions and an OPQ labeling review.

The claim for the Categorical Exclusion for the Environmental Assessment has been granted.

The Office of Process and Manufacturing Assessment (OPMA) has made a final overall **"Withhold"** recommendation for the facilities involved in this application for this review cycle.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Donepezil is a reversible inhibitor of the ecetylcholinesterase. The drug substance is donepezil hydrochloride. The reference drug, Aricept (donepezil hydrochloride) tablets, was approved in November 1996 (NDA (b) (4)) for the treatment of dementia of the Alzheimer's type in mild, moderate, and severe Alzheimer's Disease. NDA 212304 proposes a donepezil transdermal system (TDS) and relies on the pharmacokinetic comparison between the proposed TDS product and the approved Aricept tablets to support efficacy. (b) (4)

In this NDA, Corium Inc. proposes a transdermal system for once weekly application (7-day wear) to the back, buttocks, or thigh of 5.0 mg/day and 10.0 mg/day strengths (strength expression supported by residual drug analysis). In total the drug product is composed of six layers. The drug product is a rectangular, beige/tan TDS with the name and strength printed on the backing membrane. The product utilizes a blue tinted and slit release liner which is removed and discarded prior to application. The product uses an integrated overlay design in which a larger inactive laminate is adhered to a smaller active (i.e. drug containing) laminate. The

active laminate is segmented into smaller portions, resembling a grid. (b) (4)

[redacted]

Figure 1: Cross Section of ADLARITY

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)

A significant product quality and use issue was identified early in the review cycle related to the delamination (b) (4) [redacted] and can easily be separated by hand or, in some cases, by simply removing the release liner (see Figure 2 below). This concern was initially communicated to the Applicant on 14-NOV-2019 in an email and further discussed with the applicant in a Tele/Video Conference on 20-NOV-2019.

(b) (4) [redacted]

A number of potential risks have been identified arising from the separation of an active segment(s) from the remainder of the transdermal system.

- Increased risk of unintentional overdose due to an active segment remaining adhered to the skin when the product is removed from the body. The segment left on the skin may contain residual drug and continue to release drug after a new TDS is applied.
- Increased risk of underdosing and ineffective treatment if (b) (4) .
- Increased risk for potential misuse due to patient's or caregiver's application of only the drug layer or only a few of the segments of the drug layer.
- Increased risk of accidental exposure to others when the release liner is disposed of in the trash and (b) (4) .

The changes proposed to the drug product and submitted throughout this review cycle (e.g. (b) (4)) have not been shown to mitigate the ease of separation. **Specifically, none of these changes are expected to (b) (4) . Refer to CR Deficiency Number 1, the Discipline Review Letter sent May 4, 2020 (Appendix 1) and the Clarifying Email Response Sent May 29, 2020 (Appendix 2).**

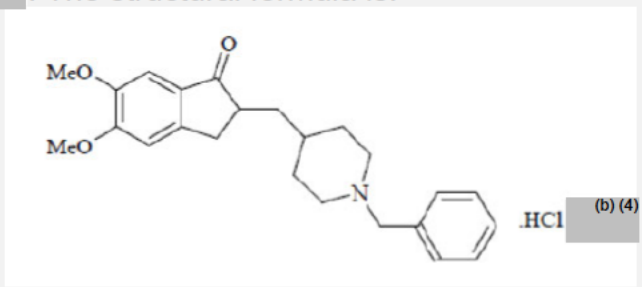
Additional significant quality deficiencies have been identified throughout the review cycle and are further discussed below.

Proposed Indication(s) including Intended Patient Population	For the treatment of dementia of Alzheimer's type in patients with mild, moderate, and severe Alzheimer's Disease.
Duration of Treatment	Applied once weekly for seven day wear. For chronic continuous use in patients with mild to severe Alzheimer's Disease.
Maximum Daily Dose	10 mg per day donepezil ((b) (4) 193.7 mg donepezil hydrochloride equivalent to 176.7 donepezil free base)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, donepezil hydrochloride, is a white to off white crystalline powder and a hydrochloride salt (b) (4). The molecular formula is $C_{24}H_{30}ClNO_3$ (b) (4). Its molecular weight is (b) (4). The structural formula is:



Four different polymorphs of donepezil hydrochloride are reported in literature. Polymorph Form (b) (4) has been characterized for the drug substance, though Form (b) (4) is the polymorph present in the finished drug product.

Two manufacturers are listed in the NDA, (b) (4), and (b) (4). Batches from both manufacturers were found to be comparable and within specification, although the manufacturing process differs significantly between the two. The DMFs for each manufacturer (DMF (b) (4) and (b) (4) respectively) are referenced for additional information and each determined to be adequate at the time of this review. The drug substance structure has been adequately characterized and is consistent with the USP monograph for donepezil hydrochloride. Ten specified impurities described in the monograph are adequately addressed in the quality control approach. The any unspecified impurity limit is set at NMT (b) (4)%, which is (b) (4) than limits for all specified impurities in the USP monograph. No mutagenic impurity risks were observed. Elemental impurities are not included in the drug substance specification with adequate justification and residual solvents are controlled with acceptable ICH limits. The manufacturing process has been sufficiently described and appears reasonable. The starting materials are at reasonable points in the synthesis for both processes and comply with ICH Q11.

Based on the stability data provided for the registration batches from the two proposed commercial manufacturers (b) (4), a proposed retest date of (b) (4) months ((b) (4)°C(b) (4)% RH) is acceptable for donepezil hydrochloride.

Drug Product: Inadequate

Donepezil transdermal system is supplied in two strengths of 5.0 mg/day and 10.0 mg/day and designed for once-weekly application. The TDS is a six layer incorporated overlay design using (b) (4)

(b) (4) and several other critical excipients. Acrylate copolymers are commonly used (b) (4), though the specific grade (b) (4) has not been utilized in an approved product previously. Given the size of the product, the majority of the excipient are at levels that exceed the FDA's Inactive Ingredient Database (IID) for TDS. However, the formulation and level of excipients have been qualified by non-clinical studies, and adequate controls of the raw materials have been provided.

(b) (4) is used in the formulation (b) (4)

. (b) (4)

of donepezil base over the seven-day TDS wear period. Note, the Applicant has been asked to develop a method quantifying the donepezil base at drug product release and during storage and to set the associated limits (method development and validation and the setting and justification of acceptance criteria is ongoing and outstanding for this review cycle).

The strength of the transdermal system is supported by the residual drug analysis from products worn in clinical trial P-15086.

Clinical Trial 15086	Donepezil HCl delivered		
	52.5 cm^2	105 cm^2	105 cm^2
Average (per day)	(b) (4)		
Average (total)			
SD (total)			
	Donepezil free base		
Average donepezil (per day)	(b) (4)		

The average donepezil free base released is ~ (b) (4) % equivalent to the following strengths: (b) (4) mg/day and (b) (4) mg/day. The Applicant proposed 5 mg/day and 10 mg/day is well within the standard deviation of the strength determined from residual drug analysis and importantly the proposed strengths maintain proportionality.

The primary packaging for the transdermal system is a (b) (4) pouch. The secondary packaging is a carton. The Applicant has provided release results for three registration batches of each strength, all of which met the proposed specifications, though several tests have been modified, or requested to be added to the specification during this review cycle. For example, given the ease with which the different laminates of the drug product could be separated the applicant was requested to develop a method for separation strength of (b) (4).

While the applicant has developed a peel adhesion method for this parameter, specification limits and justification remain outstanding.

(b) (4)

During the review cycle the applicant noted up to (b) (4) in 24 months, (b) (4) within 18 months, and approximately (b) (4) within 9 months. The applicant's provided IVPT study results seemingly indicating that (b) (4) do not play key roles in drug delivery. However, there is very larger variability in all of the results (e.g. control flux is 3.1 ± 2.5; control cumulative permeation is 505 ± 408). With high variability, it is unclear whether N-1 in-vitro skin permeation studies are capable of determining the impact of individual excipients on drug delivery. As such, release and stability testing for (b) (4) content may be necessary to ensure drug product quality over its lifetime. In addition to the delamination of the layers discussed above, the drug product has a major and overarching concern related to the stability of the product. The BE studies appeared to have utilized product no more than 6 months in age. Given the significant changes seen on stability (including in vitro release) there is an overarching concern that a product at the beginning of shelf life will not deliver the same amount of drug over 7 days as a product near the end of its shelf life.

Based on the drug product control strategies, release data, and stability results, the proposed product is **inadequate** from a drug product perspective. Refer to the full drug product review for detailed information.

Also, from a drug product perspective, refer to Complete Response Deficiencies Numbers 1, 2 and 4, and Additional Comments 7-11 to be communicated in the CR letter.

Labeling: Inadequate

The Label/Labeling of NDA 212304 was not reviewed during this review cycle. The below comment was communicated in the DRL dated 4-MAY-2020:

Finally, we have determined that the identified deficiencies preclude discussion of labeling changes and/or post marketing requirements/commitments at this time.

Environmental: Adequate

The Applicant cites 21 CFR§ 25.31 (b) indicating the estimated concentration of donepezil HCl at the point of entry into the aquatic environment will be well below 1 part per billion. Additionally, the Applicant confirms that to the best of their knowledge no extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action.

The Applicant's claim for categorical exclusion is acceptable and adequate for approval of the application.

Manufacturing: Inadequate

The drug product is manufactured by Corium Inc. in Grand Rapids, MI. (b) (4)

(b) (4)

(b) (4)

This 505(b)(2) relies on bioequivalence compared to an oral formulation. There is no in vivo data comparing the registration-scale products to the oral formulation or the BE-scale product. An in vivo BE study using the registration scale product was designed and conducted (Study P-16010), but the blood samples were not analyzed. Currently, there is no in vivo bridge from the registration-scale process to the BE-scale process.

In vitro bridging data was provided in P.2.3 Appendix 2 however several deficiencies confound the use of the in vitro bridge:

- Different storage temperatures (5°C vs (b) (4))
- Different storage times (6 months vs. new)
- Different API suppliers
- Substantially different API particle sizes

This general concern regarding the lack of in vivo bridge was communicated in the DRL and the follow-up email correspondence dated 29-MAY-2020.

Regarding Delamination/Separation

Throughout the review the applicant has proposed multiple manufacturing changes to address delamination between the layers, some formally to the eCTD making changes to module 3 and some informally (e.g. change to the (b) (4) that was not submitted to P.3). The review team concluded none of the proposed changes to date address delamination (b) (4) (b) (4) should be considered in the next review cycle if it is formally included in the resubmission.

For full details, refer to the Manufacturing and Facilities Review. Also, from a manufacturing perspective, refer to Complete Response Deficiency Number 3, and Additional Comments 4-6 to be communicated in the CR letter below.

Facilities: Inadequate

The drug substance, donepezil hydrochloride, is sourced from two manufactures 1) (b) (4) and 2) (b) (4). The Drug Product is manufactured at Corium in the USA. No PAI was requested for either the drug product or drug substance manufacturing facilities.

The drug substance, drug product, and related facilities (e.g. critical intermediates, testing sites) were evaluated. A critical DS intermediate site, (b) (4), is listed as OAI as of (b) (4). This intermediate site is utilized for the drug substance produced at (b) (4). The drug substance from (b) (4) will not be acceptable for commercial manufacturing if a withhold is recommended for this intermediate manufacturer. Notable, two out of the three registration stability batches utilized drug substance from (b) (4). Additionally, a different testing site (b) (4) was submitted in an unsolicited amendment on 04/28/2020. This site has not been evaluated, and that lack of evaluation will be communicated to the applicant. An overall withhold is recommended due to the following facility:

(b) (4)

(b) (4)

The other facilities in the submission are approvable. For full details refer to the Manufacturing and Facilities Review. Also, from a facilities perspective, refer to Complete Response Deficiency Number 5, and Additional Comments 1-3 to be communicated in the CR letter below.

Biopharmaceutics: Inadequate

The biopharmaceutics review focused on the evaluation of 1) the proposed in vitro drug release testing (IVRT) method and acceptance criteria, 2) formulation bridging, and 3) (b) (4).

IVRT Method

The provided IVRT data show that the proposed IVRT method is discriminating towards (b) (4), and a critical formulation variable (product with (b) (4)% of the targeted amount (b) (4)). The proposed drug product exhibits significant change in the quality during storage, which is detectable by the proposed IVRT method. Based on the provided information/data and justifications, as well as the demonstrated discriminating ability, the proposed IVRT method is deemed acceptable for quality control testing of the proposed drug product. Note, if significant changes to the drug product are made to address the CR deficiencies, a reassessment of the newly generated data will be performed and a new recommendation for the IVRT method will be made. Refer to additional comment #11.

Formulation Bridging

Several process related changes were made between the bio-batch and the to-be-marketed products. Per the Process Review Team, the changes in manufacturing process are significant and, consequently, an additional PK study is needed to bridge the drug product that was used in study P-15086 and the commercial product. Refer to CR Deficiency Number 2 for more detail.

(b) (4)

(b) (4)

Additional: In vitro permeation testing (IVPT)
The applicant also provided IVPT data to support that the observed changes in the drug product quality will not impact therapeutic outcome. However, the provided in vitro skin permeation data are inconclusive and the in vivo pharmacokinetics data are obtained solely from less than six months old drug product. These data are not sufficient to provide assurance that the observed decrease in the in vitro drug release rate would not affect the clinical performance of the proposed drug product throughout its shelf-life. Refer to the DP review and CR Deficiency 2 for information regarding the change in drug product's quality during its storage.

Additional Quality Discipline – In Vivo Adhesion: Adequate

From a quality perspective, the formulation of the drug product used in clinical study P-16010 and P-16012 demonstrates adequate in vivo adhesion for the prescribed 7-day wear period. Although the size of the active area differed slightly (<2%) in these studies, the overall size remained the same and no significant or negative impact related to adhesion is expected for the proposed commercial product.

The applicant has demonstrated that the probability that at least 80% of all ADLARITY TDS will maintain at least 80% surface area adhesion during the entire wear period using both the largest and smallest sizes and for all application sites (back, buttock, and thigh). As such the quality recommendation for adhesion to the Office of New Drugs of the ADLARITY (donepezil transdermal system) is APPROVABLE.

Note however, if significant changes to the product are made to address the Complete Response issues and a new adhesion study is necessitated, a new assessment of that data and a new recommendation for adhesion will be required. Refer to the CR Additional Comment #11.

Related to Separation of the Layers

While this product's delamination quality issue did not directly impact the conduct of the adhesion studies, one of the risks identified with the ease with which delamination could occur was observed during the clinical trials and can be seen in some of the photographs taken during the trial.

Week 5
96 Hours After Application

Separation observed and (b) (4) is seen peeling away - photo provided by the applicant.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Donepezil Assay/Related Substance	Formulation, raw materials, container closure, process, scale, equipment	**L**	(b) (4)	**L**	Assay does not differentiate between salt and base
(b) (4) Base Assay	Formulation (b) (4) stability, (b) (4)	**H**		**H**	No Acceptance Criterion has been established

Lauryl Lactate (LL) Content	Formulation, stability, (b) (4)	M	(b) (4)	H	(b) (4)
Sorbitan Monolaurate (SM), Triethyl Citrate (TC) Content (Tests are not currently included)	Formulation, stability, (b) (4)	M		H	(b) (4) May need control in future
Cold Flow (active area, border, pouch transfer)	Formulation, raw materials, stability	L		L	Relatively little cold flow of border observed on stability; some active area is notable but within specification (b) (4)
Adhesion (contact adhesive, border adhesive)	Formulation, raw materials, process, stability	M		L	Active area adhesion stronger than overlay adhesion; Some zippering observed for release liner peel Moderate trending observed but within specification, ranges established are not overly broad, so concern is lowered
Release Liner Removal (contact adhesive, border adhesive)					
Probe Tack (contact adhesive, border adhesive)					

Dynamic Shear			(b) (4)		
Separation Strength (Test not currently included)	Formulation, manufacturing process, stability	**H**		**H**	The applicant has not established a method or criteria; The applicant must first fix the inherent separation issue and then establish new criteria in next review cycle
Crystals	Formulation, (b) (4) stability, (b) (4)	**L**		L	(b) (4)
IVRT	Formulation; stability; (b) (4)	**L**		M	The 24-hour time point has a decrease of (b) (4)% over 24 months; 48-hour time a decrease of (b) (4)%; 168-hour time point has a decrease of (b) (4)% Largest drop appears to occur during the first 6 months of storage; though slower decrease is observed afterwards, it is important to note that the decrease across all three time points continues.

D. List of Deficiencies for Complete Response

1. (b) (4) the TDS can be easily separated (b) (4) and as such is a major product quality, use, and safety concern.

2. There is an overarching concern that the drug product on release is not equivalent to the drug product after long-term storage. Multiple changes have been observed during drug product storage under long term conditions:

(b) (4)

It is also unclear whether the donepezil salt:base ratio changes during storage. In addition to these differences, there is a significant drop in in vitro drug release results. The 24-hour time point results decrease (b) (4)% over 24 months. The 48-hour time point results decrease (b) (4)% over 24 months. The 168-hour time point results decrease (b) (4)% over 24 months. The provided in vitro skin permeation data and the limited in vivo pharmacokinetics data (of up to six-months old drug product) are not sufficient to demonstrate that the observed decrease in the in vitro drug release rate from the proposed drug product would not affect its therapeutic performance throughout the shelf-life of the proposed drug product.

We acknowledge the results provided from the *in-vitro* skin permeation studies comparing the to-be-marketed formulation to the same formulation without one of the excipients (N-1). You conclude that all results are comparable to the control, thus (b) (4) do not play a role in drug delivery. However, there is very large variability in all of the results (e.g. control flux is 3.1 ± 2.5; control cumulative permeation is 505 ± 408). With high variability, it is unclear whether N-1 *in-vitro* skin permeation studies in general are capable of determining the impact of individual excipients on drug delivery.

3. We determined that the intended commercial process has major differences compared to the process used for the pivotal clinical batch used in study #P-15086. Specifically, there have been changes in (b) (4)

for the registration batches (pg. 24 of the W38132 executed batch record in 3.2.R) but this is not evidenced for the batch used in study #P-15086. These differences could have impact on (b) (4)

(b) (4)

and could result in the variation in delivery of the active ingredient to the patients.

Further, the in vitro bridging data in the submission is inadequate to justify the above changes for the following reasons: (1) With respect to the in vitro release method, a different method at batch release was used for the batch in study #P-15086 from that for the registration batches; (2) The study and testing regarding donepezil base content was not conducted at batch release for the registration batches nor for the batch used in study #P-15086; (3) The submitted document in P.2.3 Appendix 1, Bioequivalence (BE) and Registration Product Comparison, compared batches with different manufacturing processes, API particle sizes, storage times, and storage temperatures in addition to scale changes. With all these variations, it is difficult to make a conclusive and holistic comparability assessment.

4. (b) (4)

5. During a recent inspection of the (b) (4) manufacturing facility, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional Comments to be communicated in the CR letter:

1. Sections S.2.1 and P.3.1 and sections pertaining to combination product manufacturing were not prepared in accordance with the guidance titled "Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER: Questions and Answers". Provide updated versions of these sections.

2. An incorrect FEI number was provided in the FDA Form 356h for (b) (4) . Provide an updated copy of the FDA Form 356h.

3. The 04/28/2020 amendment to the NDA included an unsolicited facility submission. This facility was not assessed during this review cycle. The assessment of this facility will be completed when the NDA is resubmitted.

4. Data was provided on 03/31/2020 to demonstrate that API particle size did not impact [redacted] (b) (4). The batches used in the study had different API particle sizes, different batch formulas, and different scales. This is inadequate for assessing the impact of API particle size alone. Provide additional studies to justify that API particle size does not impact [redacted] (b) (4) [redacted].

5. [redacted] (b) (4)

6.

7. As part of the amendment dated 10-Apr-2020, you have updated the release liner [redacted] (b) (4).
    a. Provide data demonstrating that the [redacted] (b) (4) is robust ([redacted] (b) (4) [redacted]) and remains unchanged during storage (e.g. [redacted] (b) (4) [redacted]).
    b. Provide any release and stability results for drug product manufactured with the newly proposed release liner.

8. The pouch seal strength acceptance criteria (NLT [redacted] (b) (4) psi for the 5 mg/day strength and NLT [redacted] (b) (4) psi for the 10 mg/day strength) is based a combination of release and stability data for registration and supportive stability batches, including extrapolation of data from 12 months onward. There is now real time data available up to 24 months for both drug product strengths. Tighten the pouch seal strength limits based on all available release and stability data for the primary registration batches.

9. As part of the microscopic crystal inspection you observed the presence of crystals, [redacted] (b) (4) in the primary registration batch 38132B. [redacted] (b) (4) [redacted]

(b) (4)

(b) (4) Clarify.

10. We note that you have committed to addressing the following questions, but responses are currently pending:
    a. Question 2 from 31-Dec-2019 Information Request: Develop a method for the separation strength of (b) (4)). Monitor separation strength on release and stability of the drug product. Set and justify the associated acceptance criterion.
    b. Question 6b from 31-Dec-2019 Information Request: Provide a comparison of the donepezil free base and donepezil HCl content in the clinical drug product batches to the registration drug product batches.
    c. Question 3 from 9-Mar-2020 Information Request: Results from the ICH Q1B photostability study indicates that the unpouched drug product is impacted by exposure to light. Perform an in-use stability study to demonstrate that the drug product quality remains unaffected through the longest expected period of use (7 days) at lowest dose (5 mg/day). Ensure that the drug product is exposed to light (e.g. 10 hours a day) each of the seven days to mimic a worst-case scenario.

11. If in order to address the deficiencies identified in the Complete Response significant changes are made to the product (e.g. formulation, design, size) additional studies such as in vivo adhesion studies, or redevelopment of some quality test methods and acceptance criteria may be necessitated.

Application Technical Lead Name and Date:
Caroline Strasinger, PhD
CDER/OPQ/ONDP/DNDP2
19-JUN-2020

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Caroline Strasinger

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NDA 212304

CHAPTERS: Primary Quality Assessment

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BIOPHARMACEUTICS

Application No: NDA 212304; 505(b)(2)
Drug Product Name/Strengths: ADLARITY™ **(**Donepezil HCl) Transdermal System; 5 mg/day equivalent, 10 mg/day equivalent
Route of Administration: Transdermal
Indication: Treatment of Dementia of the Alzheimer's Type
Applicant Name: Corium, Inc.
Date of Submission: 09/30/2019 (Original)

Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Ta-Chen Wu, PhD

REVIEW SUMMARY

Submission: The Applicant submitted the current 505(b)(2) NDA for ADLARITY™ **(**Donepezil HCl) Transdermal System (TDS; also referred as Corplex^{TM} Donepezil TDS by the Applicant); 5 mg/day equivalent, 10 mg/day equivalent, with reliance on the prior safety and efficacy findings of the Agency for the Listed Drug (LD) ARICEPT (donepezil hydrochloride) Tablets (NDA 020690, approved on 11/25/1996). The proposed TDS drug product, applied once a week for 7-days, is indicated for the treatment of dementia of the Alzheimer's type. The ADLARITY™ 5 mg/day adhesive patches are rectangular in shape, with rounded corners, measuring 8.3 cm by 10.8 cm, and containing 97 mg of donepezil HCl. The ADLARITY 10 mg/day adhesive patches are rectangular in shape, with rounded corners, measuring 10.8 cm by 14.4 cm, and containing 194 mg of donepezil HCl.

Review Objective: The Biopharmaceutics review is focused on the evaluation of (1) the proposed in vitro drug release testing (IVRT) method and acceptance criteria, (2) formulation bridging, and (3) (b) (4).

IVRT Method: The Applicant conducted studies and provided justifications for selection of the suitable IVRT testing conditions. The proposed IVRT method for the proposed TDS drug product is as follows: *900 mL of 0.02 M Sodium Acetate Buffer, pH 4.5, using USP Apparatus 5 (Paddle over Disk) with Transdermal System Holding Wire Screen (TSHWS) at 100 rpm*. The provided IVRT data show that the proposed IVRT method is discriminating towards (b) (4), a critical process parameter (CMA), and towards critical formulation variable (product with (b) (4) % of the targeted amount (b) (4)). The proposed drug product exhibits significant change in the quality during its storage, which is detectable by the proposed IVRT method. Based on the provided information/data and justifications, as well as the demonstrated discriminating ability, the proposed IVRT method is deemed acceptable for quality control testing of the proposed drug product.

The Applicant provided in vitro skin permeation data and limited in vivo pharmacokinetics data to support that the observed change in the drug product's quality during its storage will not affect the therapeutic outcome. However, the provided in vitro skin permeation data are inconclusive and the in vivo pharmacokinetics data are obtained solely from less than six months old drug product. These

data are not sufficient to provide assurance that the observed decrease in the in vitro drug release rate would not affect the clinical performance of the proposed drug product throughout its shelf-life. The concerns regarding the change in drug product's quality during its storage will be conveyed to the Applicant by Drug Product Review Team. If significant changes to the drug product will be made by the Applicant to address the Complete Response deficiencies, a reassessment of the newly generated data will be performed and a new recommendation for the IVRT method will be made.

IVRT Acceptance Criteria: The Applicant's proposed acceptance criteria are as follows: 1 Hour: NMT (b) (4); 8 Hours: (b) (4)%; 24 Hours: (b) (4)%; 48 Hours: NLT (b) (4)%; 168 Hours: NLT (b) (4)%. The Applicant's proposed acceptance criteria will be reviewed once the concerns regarding the change in drug product's quality during its storage are addressed by the Applicant.

Formulation Bridging: Several process related changes were made between the bio-batch and the to-be-marketed products. Per the Process Review Team, the changes in manufacturing process are significant and, consequently, an additional PK study is needed to bridge between the drug product that was used for the study 15086 and the commercial product.

(b) (4)

RECOMMENDATION: From a Biopharmaceutics perspective, NDA 212304 for ADLARITY™ (Donepezil HCl) Transdermal System, 5 mg/day equivalent and 10 mg/day equivalent, is inadequate due to the outstanding deficiencies regarding the change in drug product's quality during storage, formulation bridging, and comparative IVRT data for the two strengths. The following Biopharmaceutics deficiencies should be conveyed to the Applicant:

Biopharmaceutics Deficiency for the Complete Response Letter:

(b) (4)

BIOPHARMACEUTICS ASSESSMENT

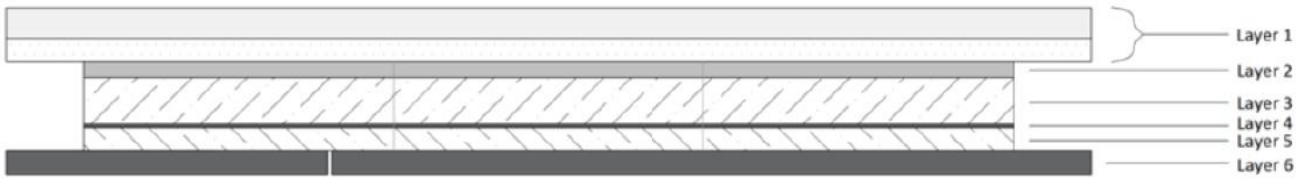
LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	09/30/2019	Original NDA Submission
0007	01/10/2020	Quality/Response to Information Request
0009	02/07/2020	Quality/Response to Information Request

BACKGROUND

The proposed drug product is a once-weekly system for the transdermal administration of donepezil with two different drug product strengths of 5 mg/day and 10 mg/day. The composition of the proposed drug product is provided in Appendix 1. The TDS is comprised of six layers (Figure 1). The two strengths of the proposed TDS of matrix formulation are compositionally equivalent, (b) (4) and varied only in their sizes. The differences in dose are obtained by the proportional increases in the surface area (size) of the TDS between 52.5 cm^2 and 105 cm^2 (Table 1).

Figure 1. Cross-Sectional View of the proposed Donepezil TDS



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)

To support the 505(b)(2) NDA, the Applicant conducted a PK bridging study [a relative bioavailability (BA) study (Study P-15086) at steady state] between the 10mg/day strength of the proposed TDS and Aricept® Tablets, 10 mg (refer to EOP2 meeting on August 22, 2017 and its follow-up meeting).

The Biopharmaceutics review is focused on the evaluation of what the Applicant submitted in the current NDA in support of the approval of: (1) the proposed in vitro drug release testing (IVRT) method and acceptance criteria, (2) formulation bridging, and (3) (b) (4) .

PROPOSED IVRT METHOD AND METHOD DEVELOPMENT

Biopharmaceutics recommendation related to the in vitro drug release testing (IVRT) method, acceptance criteria and data submission were provided to the Applicant during the IND stage (IND 129778). In the current submission, the Applicant has provided information/data and justified the selection of the proposed IVRT method (Method AM 256) for quality control testing of the proposed drug product [Module 3.2.P.2.2. Section 3.7 (Page 81/93)]. The Applicant's originally proposed IVRT method and acceptance criteria are summarized in Table 1.

Table 1: IVRT method and acceptance criteria originally proposed by the Applicant

Apparatus	USP Apparatus 5 (Paddle over Disk) with Transdermal System Holding Wire Screen (TSHWS)
Paddle Speed	100 rpm
Volume	900 mL
Medium	0.02 M Sodium Acetate Buffer, pH 4.5
Temperature	32.0 ± 0.5°C
Acceptance Criteria	1 Hour: NMT (b)(4)% 8 Hours: (b)(4)% 24 Hours: (b)(4)% 48 Hours: NLT (b)(4)% 168 Hours: NLT (b)(4)%

(b) (4)

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(b) (4)

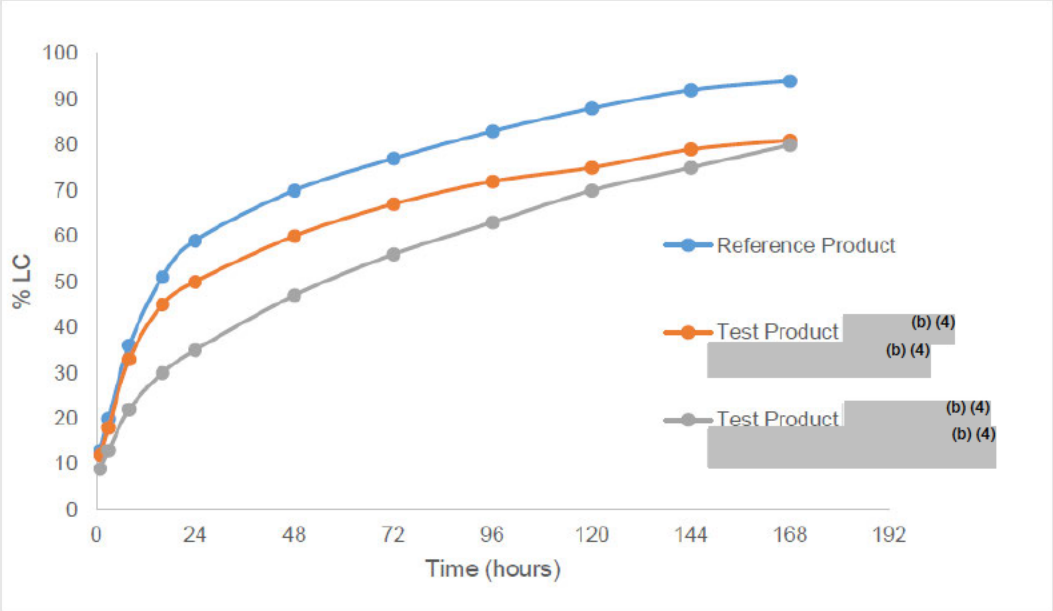
Discriminating Ability of the IVRT Method AM256

First, the method's discriminatory nature was evaluated in a preliminary study where the reference product (target) was compared against test products manufactured with intentional variations in two of the critical manufacturing variables as follows:

- (b) (4)
-

The results from the study (Figure 5) indicate the method can discriminate between the reference and test products. The (b) (4) test product was comparable to the reference product at the initial timepoints but yielded noticeably lower release by the 24-hour timepoint. The (b) (4) test product started with a much slower drug release, and eventually ended at a cumulative release at the final timepoint similar to the (b) (4) test product.

Figure 5: Drug Release Preliminary Discriminatory Testing of [redacted] and [redacted] Corplex Donepezil TDS Test Products



(1) Drug release test conditions: USP Apparatus 5 with TSHWS, @100rpm, 900 mL 0.02M Sodium Acetate pH 4.5, @32°C

After the preliminary discriminatory studies, additional discriminatory drug release studies were subsequently carried out with the 0.02 M SA buffer pH 4.5 using test products that were intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables, as described below:

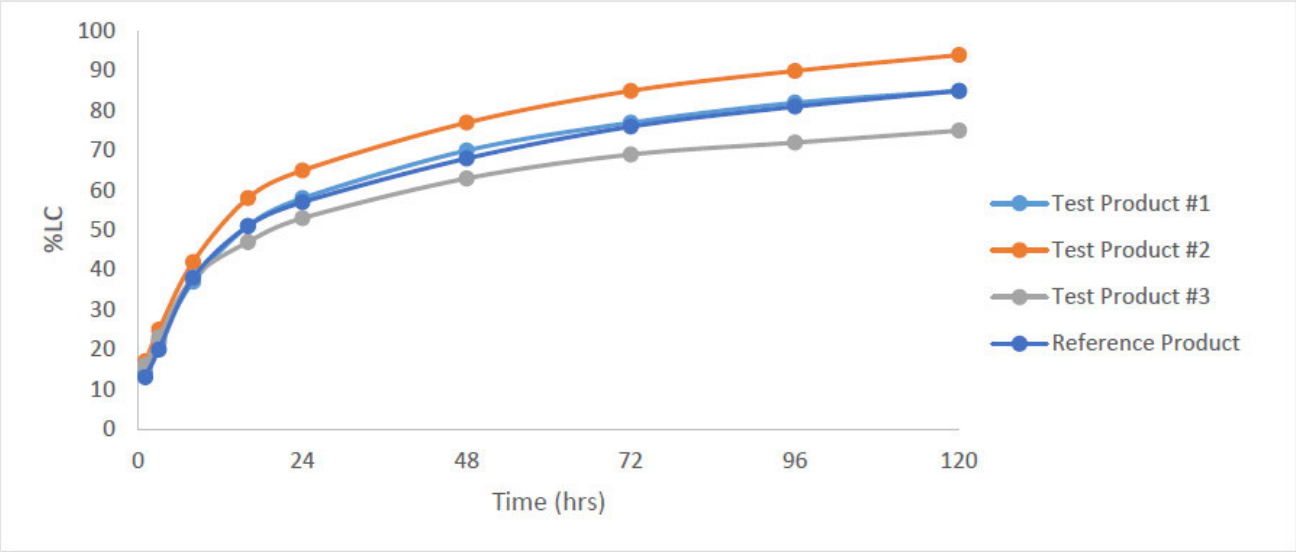
Test Product 1 - [redacted]: a product not [redacted] as required to manufacture [redacted] of the drug product [see Figure 1 [redacted]

Test Product 2 - [redacted] - a product manufactured with [redacted] of the drug product at [redacted] than target [see Figure 1 [redacted]

Test Product 3 - [redacted] - a product manufactured with drug matrix layer of the drug product at [redacted] than target [see Figure 1, [redacted]

The results from the study (Figure 6) indicate that the proposed IVRT method can discriminate between the study reference and test products. The drug release profile of the product with the [redacted] (test product 3) was comparable to the profile of the study reference product at the initial timepoints but yielded noticeably lower release after the 24-hour timepoint. The drug release profile of the product with [redacted] (test product 1) was identical to the profile obtained for study reference product. The drug release profile of the product with the [redacted] (test product 2) was comparable to the profile of the reference product at the initial timepoints but yielded noticeably higher release after the 16-hour timepoint.

Figure 6: Additional Discriminatory Release Studies with Method AM256



(1) Drug release test conditions: USP Apparatus 5 with TSHWS, @100rpm, 900 mL 0.02M Sodium Acetate pH 4.5, @32°C

The provided data indicate that the proposed IVRT method is adequately selected and is discriminating towards relevant critical attributes/variables. The paddle rotation speed of 100 rpm is not common with USP Apparatus 5; however, the Applicant's selection of the paddle speed is justified and supported by the provided data. The proposed IVRT method is deemed adequate for QC testing of the proposed drug product.

IVRT ACCEPTANCE CRITERIA

IVRT Data for the Registration and Clinical Batches

The Applicant provided full-profile IVRT data from the BE lot 37277B collected after 9-months of storage at 5ºC (Table A of Appendix 2). The Applicant did not collect IVRT data at the time of batch-release as the Applicant was using a different IVRT method at that time (Method ATP179), and the currently proposed method (AM256) was not developed. The Applicant provided full-profile IVRT data for the registration batches (38132B, 38442B and 38656B) collected at the time of batch-release (T=0), as summarized in Tables B-D of Appendix 2.

The provided data indicate that the drug release rate from the BE batch (collected after 9-months of storage at 5ºC) was slower than those from the registration batches collected at the time of batch-release. Similarly, the rate of drug release was decreasing consistently during the stability testing period. The provided drug release data collected at T= 0 and during the long-term stability testing period from the registration lots indicate that the maximum cumulative drug releases at the last time-point (7 days/168 hours) are in the range of 91-101% at T=0; however, these values drop steadily to up to 75% during the stability testing period. The Applicant was asked to investigate the root-cause of this issue. In response (dated 02/07/2020), the Applicant provided an investigation report which indicates that the observed decrease in the drug release rate was due to (b) (4) . The provided information/data from the investigation report submitted on 02/07/2020 indicate that the proposed drug product exhibits a significant change in its quality during its storage/shelf-life. (b) (4) . The provided in vitro skin permeation data are inconclusive and the in vivo pharmacokinetics data are obtained only from less than six months old drug product. These data are not sufficient to provide assurance that the observed decrease in the in vitro drug release rate would not affect the clinical performance of the proposed drug product throughout its shelf-life. The Applicant was requested (via an IR dated 03/09/2020) to take appropriate measure to address the quality issue of reduction in the in vitro drug release rate from the proposed drug product during its storage/aging. However, the Applicant re-submitted the information/data that they had previously submitted and did not adequately address the quality issue identified. A discipline review letter was sent to the Applicant by OPQ on 05/04/2020 regarding the changes observed during drug product storage under long term conditions as well as the outstanding concerns for the intended commercial process being significantly different compared to the process used for the pivotal clinical batch used in study #P-15086 and the ease of separation (b) (4).

In the original submission, the Applicant provided wider ranges of drug release acceptance criteria (Table 2) (b) (4) Via an IR dated 03/09/2020, the Applicant was reminded that the in vitro drug release acceptance criteria are set based on the drug release profile from freshly manufactured batch used in the bioequivalence/clinical study. In general, the selection of the in vitro drug release acceptance criteria ranges is based on mean target value ±10% (for example, a range of 40-60% for the mean value of 50%). Wider acceptance criteria ranges may be acceptable only if appropriately justified with clinical/IVIVC data. In response to the IR, the Applicant proposed wider acceptance criteria, as shown below, but did not address the issues pertaining to the product quality. Therefore, the acceptance criteria for the proposed dur product will be reviewed after the quality issues are addressed.

Table 2: Proposed Drug Release Acceptance Criteria

Time	Original Proposed Acceptance Criteria	Revised Proposed Acceptance Criteria
1 hr	NMT (b) (4)%	NMT (b) (4)%
8 hr	(b) (4)%	(b) (4)%
24 hr	(b) (4)%	(b) (4)%
48 hr	NLT (b) (4)%	NLT (b) (4)%
168 hr	NLT %	NLT %

FORMULATION BRIDGING

The differences between the formulations used in the bioequivalence study and the final to-be-marketed formulation are as follows:

- (b) (4)

The Applicant provided in vitro drug release, in vitro skin permeation, and batch release and stability data to support these changes. However, it is important to note that a different IVRT method was used at the time of batch release for bio-batch from that for the registration batches. The Drug Process Reviewer notes that the submitted document in P.2.3 Appendix 1, Bioequivalence (BE) and Registration Product Comparison, compared batches with different manufacturing processes, API particle sizes, storage times, and storage temperatures in addition to scale changes. With all these variations, it is difficult to perform a conclusive and holistic comparability assessment. These concerns were conveyed to the Applicant by the Process Reviewer via the discipline review letter dated 05/04/2020. Per the Process Review Team, the changes in manufacturing process are significant and an additional PK bridge is needed between the product used in study 15086 and the commercial product used in studies 16010, 16012.

(b) (4)

(b) (4)

Bioequivalence: The Applicant provided results of the study P-15086 and claimed bioequivalence between the higher strength (10 mg/day) of the proposed drug product and the LD product. As per the Clinical Pharmacology Review, bioequivalence was established at steady state between Once-Weekly Donepezil TDS and the LD Aricept®. Both $C_{max,ss}$ and $AUC_{0\text{-}tau}$ met the statistical criteria for BE in the "pivotal" study P-15086 over the one-week dosing interval. Since the manufacturing process used for the product in study P-15086 is not the same as the proposed manufacturing process for the commercial product and this change in the manufacturing process is significant, an in vivo PK bridging study is needed between the drug product that was used for 15086 and the commercial product (i.e. the product used for studies 16010, 16012). The office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 212304 and finds it not acceptable from an OCP perspective.

Strength Proportionality: The two strengths of the proposed drug product (5 mg/day and 10 mg/day) (b) (4) differ only in the size. Therefore, these two strengths of the proposed drug product are considered as dose proportional.

In vitro Release Comparison: The Applicant provided in vitro drug release profile comparison between the higher strength (10 mg/day; bio-batch) and the lower strength (5 mg/day) TDS products, generated using the proposed IVRT method. The Applicant performed similarity factor (f2) comparison between the bio-batch and each of the registration-scale batches for the lower strength (b) (4). The bioequivalence batch used in the comparison was 9-month stability pull at 5°C (the original release method, ATP-179, was modified as AM256 and used in stability study). The Applicant did not provide information of ages (a confounding factor) of the 5 mg/day strength batches used in this study. The stability study results for the proposed drug product indicate that the quality of the proposed drug product changes significantly during its storage. The Applicant will be recommended to provide comparative IVRT data collected at the batch release to test the similarity in drug release profiles between the 5 mg/day and 10 mg/day strengths.

Dose Proportionality: As per the Clinical Pharmacology Review, "dose proportionality was established from ADLARITY TDS 50 cm^2 to ADLARITY 130 cm^2 including ADLARITY TDS 105 cm^2 using power model assessment."

(b) (4)

Appendix 1

Composition of the proposed drug product

Functional Layer (Layer No.)	Chemical Name of Excipient/Component	Quality Standard	Function	TDS Composition % (w/w) [1]
Overlay Backing/ Adhesive (Layer 1)	[redacted]	[redacted]	[redacted]	(b) (4)
Separating Layer (Layer 2)				
Drug Matrix (Layer 3)				
Microporous Membrane (Layer 4)				
Contact Adhesive (Layer 5)				
Release Liner (Layer 6)				

Appendix 2

IVRT Data for the Registration and Clinical Batches

Table A. Individual Drug Release Data for Corplex Donepezil TDS BE Lot 37277B

%LC	Time (hr.)										
Patch #	**1**	**3**	**8**	**16**	**24**	**48**	**72**	**96**	**120**	**144**	**168**
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Average[3]	12	18	33	48	55	67	76	82	87	91	94
%RSD[3]	1.5	1.6	1.9	1.4	1.9	2.2	2.4	2.4	2.2	2.2	2.1

[1] Drug release test conditions: USP Apparatus 5 with TSHWS, @100rpm, 900 mL 0.02M Sodium Acetate pH 4.5, @32°C

[2] n=12 individual dosage units were tested after ~9 months of storage @5°C

[3] Average and %RSD calculated from original full significant figure data not from rounded values in this table.

Table B. IVRT Results for Donepezil TDS Registration Stability Lot 38132B (T=0)

%LC	Time (hr)										
Patch #	**1**	**3**	**8**	**16**	**24**	**48**	**72**	**96**	**120**	**144**	**168**
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Average[2]	18	24	40	53	59	70	77	82	86	89	92
%RSD[2]	4.5	3.1	2.6	2.0	2.1	2.1	1.6	1.6	1.3	1.3	1.1

[1]Drug release test conditions: USP Apparatus 5 with TSHWS, @100rpm, 900 mL 0.02M Sodium Acetate pH 4.5, @32°C

Table C. IVRT Results for Donepezil TDS Registration Stability Lot 38442B (T=0)

%LC	Time (hr)										
Patch #	**1**	**3**	**8**	**16**	**24**	**48**	**72**	**96**	**120**	**144**	**168**
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Average[2]	16	25	44	58	66	80	87	92	96	99	101
%RSD[2]	5.5	4.3	3.1	2.5	2.3	2.3	2.1	2.2	2.0	2.1	2.0

[1]Drug release test conditions: USP Apparatus 5 with TSHWS, @100rpm, 900 mL 0.02M Sodium Acetate pH 4.5, @32°C

Table D. IVRT Results for Donepezil TDS Registration Stability Lot 38656B (T=0)

%LC	Time (hr)										
Patch #	**1**	**3**	**8**	**16**	**24**	**48**	**72**	**96**	**120**	**144**	**168**
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Average[2]	19	27	45	58	64	77	85	91	95	97	100
%RSD[2]	4.9	3.8	2.4	1.6	1.5	1.2	1.5	1.3	1.1	1.1	1.0

[1]Drug release test conditions: USP Apparatus 5 with TSHWS, @100rpm, 900 mL 0.02M Sodium Acetate pH 4.5, @32°C

Kaushalkumar Dave

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Ta-Chen Wu

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CHAPTER VIII: ADDITIONAL QUALITY DISCIPLINE

Quality In Vivo Adhesion Assessment

Product Information	
NDA Number	212304
Assessment Cycle Number	1
Drug Product (DP) Name / Strength	ADLARITY (Donepezil)Transdermal System 5 mg/day; 10 mg/day
Route of Administration	Transdermal
Drug Product Manufacturer	Corium
Proposed Indication	Treatment of dementia associated with Alzheimer's

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original (0001)	**30-SEP-2019**
IR Response (0004)	**20-DEC-2019**
IR Response (0007) (Photos)	**10-JAN-2020**

CQAs For Review Cycle #1	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle # 1	Comments
in-vivo adhesion	H	Adhesion is critical for efficacy and safety.	H	The applicant has demonstrated that at least 80% of all ADLARITY TDS will maintain at least 80% surface area adhesion for the duration of wear. Separation (b) (4) was noted.

				Depending on how the CR issues are addressed a new adhesion study may be necessitated.

Conclusion and Recommendation:

From a quality perspective, the formulation of the drug product used in clinical studies P-16010 and P-16012 demonstrate ADEQUATE in vivo adhesion for the prescribed 7-day wear period. The quality recommendation to the Office of New Drugs for adhesion of ADLARITY (donepezil) transdermal system as formulated in this original submission is APPROVABLE.

Note, if in order to address the issues identified in the Complete Response the applicant makes a significant change to the product which necessitates the need for a new adhesion study, a new assessment of that data and a new recommendation for adhesion will be required.

Background: The purpose of this review is to assess the in vivo adhesion performance of ADALARITY (donepezil) transdermal system. To support the adhesion of the proposed product the Applicant performed studies P-15086, P-16007, P-16010, and P-16012, with the latter two being the primary studies. A reviewer generated summary of the studies is provided below for reference.

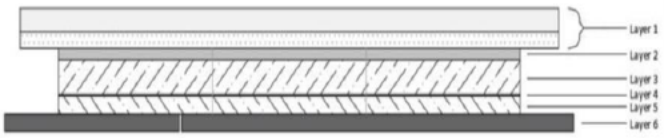
Study Number Report Link	Size and Lot Number	Number of Subjects	Number of TDS Applications	Study Notes
16012	107cm; 38090B	~60 crossover	60, 61, 62 (respectively per site)	back, thigh, buttock NMT 1 shower per day; told not to try and reapply or press it back in place; 2 subjects taped; 10% scoring increments
16010	53.5 cm (week 1) 38090; 107 cm (week 2 through 5) 38090B	~78 (8 non-completers)	214 of 53.5 cm; 209 of 107 cm	Back application; No tape or smoothing permitted in week 5; (however no tape was actually applied at any point in the study); 10% scoring
15086 – Supportive for small size	50cm2 (37569A and 37545)		91 (all treatments can be pooled)	Back application; study was done for API comparison, slightly smaller size than commercial; 4 point scale used; All scores were 0 or 1
16007 -	Treatment B is closest to Commercial	8		

Note that the size of the product's active area studied in studies 16012 and 16010 was 107cm^2 which is <2% larger that the proposed commercial size's active area (105cm^2). Use of batch 38090B for adhesion studies was agreed to in a meeting prior to NDA submission on 31-OCT-2018.

The focus of this review will be on studies 16012 and 16010. The Office of Biostatistics has assessed all data from all studies and a high-level summary of their review is also provided below.

Product Design:

Figure 1 Cross-Sectional View of the Corplex Donepezil TDS (Not to Scale)



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)

[1] The overlay border for both patch strengths is of the same width (approximately 1 cm). Therefore, although the active delivery area of the 10 mg/day patch is 2x that of the 5 mg/day patch, the total patch area is slightly less than 2x.

Figure 3 Corplex Donepezil TDS 10 mg/day Top View with Dimensions (Active Delivery Area, 105 cm^2)

(b) (4)

The drug product is proposed in two strengths 5 mg/day and 10 mg/day, utilizes an integrated overlay design, and a unique grid system (segmentation) (b) (4) . (b) (4) . The drug product is intended to be worn for 7 days on the back (lower and upper), buttocks, and thigh. The dimensions of each strength/size can be seen below:

Strength	Active Area Size	Total Size
5 mg/day	52.5 cm^2 (~8.70 cm x 6.19 cm)	86.2 cm^2 (~10.81 cm x 8.39 cm)
10 mg/day	105 cm^2 (~12.31 cm x 8.75 cm)	151.2 cm^2 (~14.4 cm x 10.95 cm)

A product use issue was identified early in the review cycle related to delamination (b) (4) While this product's quality issue does not directly impact the conduct of the adhesion studies, one of the risks associated with the ease with which delamination occurred was observed during the clinical trials and can be seen in some of the photographs taken during the trial (Figure 1b).

Figure 1: Photographs of (donepezil) transdermal system (a) ease of separation of the segments during removal of the release liner - photo provided by the reviewer; (b) separation observed and (b) (4) is seen peeling away - photo provided by the applicant.

a)

Week 5
96 Hours After Application

b)

Adhesion Study Design:

Study P-16010 was designated as the primary adhesion study. This was an open label, randomized 2 period, multiple dose study in 86 healthy male and females. Treatment A was the transdermal arm and consisted of a lead in dose of 5 mg/day (53.5 cm^2) followed by 4 consecutive weeks of 10 mg/day (107 cm^2). Subjects conducted normal daily activity, including 1 shower per day but were requested to refrain from vigorous physical activities and were not to wear tight clothing (e.g. bra, waistband that might impact the TDS). Subjects were instructed not to remove, reapply or press the system back into place should it become loose or detached. The clinical unit staff applied the TDS to the subject's back and applied firm pressure over the product for approximately 20 seconds. The protocol allowed for taping in 4 of the 5 weeks, however, no tape was applied at any point in the study to any subject. A total of 424 systems were applied and 423 were included in the adhesion population. Adhesion was graded every 12 hours after application based on % area adhered to the skin. A clear template was used to assist with scoring which used the following 0 to 11 numeric scale:

APPEARS THIS WAY ON ORIGINAL

Table 31: Adhesion Assessment Scale

Adhesion Measurement	Estimated Percent Adhered	Scoring Scale
100%	100%	0
90% to <100%	95%	1
80% to <90%	85%	2
70% to <80%	75%	3
60% to <70%	65%	4
50% to <60%	55%	5
40% to <50%	45%	6
30% to <40%	35%	7
20% to <30%	25%	8
10% to <20%	15%	9
>0% to <10%	5%	10
Detached	0%	11

Study P-16012 was a study with similar conduct in 66 healthy subjects (59 completers) but randomized into an application site sequence of back, thigh, buttock. Each week of the 3 week cross-over, a 10 mg/day system was applied to a new location. In total 186 TDS were applied and 183 were included in the adhesion population. The same scoring system as above based on % adhesion was utilized.

Reviewer's Assessment:

Studies P-16010 and P-16012 were adequately conducted to assess adhesion. Both studies assessed the largest size, permitted daily showering, instructed individuals not to purposely re-adhere the product, did not tape the system and collected multiple equally spaced time points based on % surface area adherence.

Additionally, P-16010 conducted one week of wear on the smaller size, and P-16012 assessed the adhesion of the largest size at all proposed application sites.

Applicant's Summary of Adhesion Data

Note: The applicant analyzed both adhesion studies using a mean score analysis approach. While mean score analysis is useful in a non-inferiority type study (such as those utilized for ANDAs) the mean score provides little useful analysis without a comparator. The applicant has provided frequency distributions of adhesion scores by time point which is presented below. Additionally, the applicant analyzed the systems as "Whole Patch Adhesion" and "Drug Delivery Area Adhesion" based on the integrated overlay design. In the discussion below, the analysis is of the "Whole Patch Adhesion" unless otherwise noted. In general, the applicant states the adhesion of the "Drug Delivery Area" was always greater than that of the "Whole Patch," meaning, when lift was reported it was most frequently along the periphery of the inactive overlay.

P-16010

For the 5 mg/day system, 75 of 85 TDS (88.2%) were at least 90% adhered (score of 0 or 1) through the end of the wear period and 94.1% were at least 80% adhered through 7 days. No 5 mg/day systems fully detached.

For the 10 mg/day system, 281 of 338 (83.2%) were at least 90% adhered through the wear period and 318 of 338 (94.1%) were at least 80% adhered throughout the wear period. Only 4 of 338 (1.2%) were less than 50% adhered at some point during the 7-day period. The average time to first occurrence of less than 50% adherence was 5.9 days. No 10 mg/day TDS fully detached.

Table 19: Adhesion Score Frequency Summary for the Whole Patch – (Study P-16010, Adhesion Population)

TDS Application Week (TDS Dose)	Number of Patches (n)	Hours Post Patch Application	Corplex Donepezil TDS Whole Patch Adhesion Score[a] (N = 85)									
			0	1	2	3	4	5	6	7	8	≥ 9
Week 1 (5 mg/day) TDS Applied on Day 1	85	TDS-App	85 (100%)	0	0	0	0	0	0	0	0	0
		12 Hrs	83 (97.6%)	1 (1.2%)	1 (1.2%)	0	0	0	0	0	0	0
		24 Hrs	76 (89.4%)	8 (9.4%)	0	1 (1.2%)	0	0	0	0	0	0
		36 Hrs	71 (83.5%)	13 (15.3%)	0	1 (1.2%)	0	0	0	0	0	0
		48 Hrs	60 (70.6%)	24 (28.2%)	0	1 (1.2%)	0	0	0	0	0	0
		60 Hrs	54 (63.5%)	29 (34.1%)	0	1 (1.2%)	1 (1.2%)	0	0	0	0	0
		72 Hrs	49 (57.6%)	34 (40.0%)	0	1 (1.2%)	1 (1.2%)	0	0	0	0	0
		84 Hrs	38 (44.7%)	41 (48.2%)	3 (3.5%)	1 (1.2%)	2 (2.4%)	0	0	0	0	0
		96 Hrs	36 (42.4%)	43 (50.6%)	3 (3.5%)	1 (1.2%)	2 (2.4%)	0	0	0	0	0
		108 Hrs	30 (35.3%)	49 (57.6%)	3 (3.5%)	1 (1.2%)	2 (2.4%)	0	0	0	0	0
		120 Hrs	22 (25.9%)	57 (67.1%)	3 (3.5%)	1 (1.2%)	2 (2.4%)	0	0	0	0	0
		132 Hrs	18 (21.2%)	60 (70.6%)	3 (3.5%)	2 (2.4%)	2 (2.4%)	0	0	0	0	0
		144 Hrs	15 (17.6%)	62 (72.9%)	4 (4.7%)	2 (2.4%)	2 (2.4%)	0	0	0	0	0
		156 Hrs	12 (14.1%)	63 (74.1%)	5 (5.9%)	3 (3.5%)	2 (2.4%)	0	0	0	0	0
		168 Hrs	12 (14.1%)	63 (74.1%)	5 (5.9%)	3 (3.5%)	2 (2.4%)	0	0	0	0	0
Week 5 (10 mg/day) TDS Applied on Day 29	83	12 Hrs	60 (72.3%)	23 (27.7%)	0	0	0	0	0	0	0	0
		24 Hrs	46 (55.4%)	37 (44.6%)	0	0	0	0	0	0	0	0
		36 Hrs	37 (44.6%)	46 (55.4%)	0	0	0	0	0	0	0	0
		48 Hrs	24 (28.9%)	58 (69.9%)	1 (1.2%)	0	0	0	0	0	0	0
		60 Hrs	18 (21.7%)	62 (74.7%)	3 (3.6%)	0	0	0	0	0	0	0
		72 Hrs	11 (13.3%)	66 (79.5%)	5 (6.0%)	0	1 (1.2%)	0	0	0	0	0
		84 Hrs	7 (8.4%)	69 (83.1%)	6 (7.2%)	0	1 (1.2%)	0	0	0	0	0
		96 Hrs	3 (3.6%)	71 (85.5%)	8 (9.6%)	0	1 (1.2%)	0	0	0	0	0
		108 Hrs	2 (2.4%)	71 (85.5%)	9 (10.8%)	0	1 (1.2%)	0	0	0	0	0
		120 Hrs	1 (1.2%)	72 (86.7%)	8 (9.6%)	0	2 (2.4%)	0	0	0	0	0
		132 Hrs	1 (1.2%)	71 (85.5%)	9 (10.8%)	0	2 (2.4%)	0	0	0	0	0
		144 Hrs	1 (1.2%)	69 (83.1%)	10 (12.0%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0	0	0	0
		156 Hrs	1 (1.2%)	68 (81.9%)	10 (12.0%)	2 (2.4%)	1 (1.2%)	1 (1.2%)	0	0	0	0

		168 Hrs	0	69 (83.1%)	9 (10.8%)	2 (2.4%)	2 (2.4%)	0	1 (1.2%)	0	0	0
Weeks 2 to 5[b] (10 mg/day) Combined	338	12 Hrs	248 (73.4%)	89 (26.3%)	1 (0.3%)	0	0	0	0	0	0	0
		24 Hrs	200 (59.2%)	134 (39.6%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	0	0	0
		36 Hrs	146 (43.2%)	185 (54.7%)	4 (1.2%)	1 (0.3%)	2 (0.6%)	0	0	0	0	0
		48 Hrs	103 (30.5%)	226 (66.9%)	5 (1.5%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	0	0
		60 Hrs	77 (22.8%)	247 (73.1%)	10 (3.0%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	0	0
		72 Hrs	53 (15.7%)	268 (79.3%)	12 (3.6%)	2 (0.6%)	2 (0.6%)	1 (0.3%)	0	0	0	0
		84 Hrs	40 (11.8%)	277 (82.0%)	16 (4.7%)	2 (0.6%)	2 (0.6%)	0	1 (0.3%)	0	0	0
		96 Hrs	25 (7.4%)	281 (83.1%)	25 (7.4%)	2 (0.6%)	4 (1.2%)	0	1 (0.3%)	0	0	0
		108 Hrs	20 (5.9%)	280 (82.8%)	31 (9.2%)	2 (0.6%)	3 (0.9%)	1 (0.3%)	1 (0.3%)	0	0	0
		120 Hrs	16 (4.7%)	279 (82.5%)	32 (9.5%)	3 (0.9%)	5 (1.5%)	2 (0.6%)	1 (0.3%)	0	0	0
		132 Hrs	12 (3.6%)	273 (80.8%)	40 (11.8%)	5 (1.5%)	5 (1.5%)	2 (0.6%)	1 (0.3%)	0	0	0
		144 Hrs	6 (1.8%)	273 (80.8%)	44 (13.0%)	5 (1.5%)	5 (1.5%)	3 (0.9%)	2 (0.6%)	0	0	0
		156 Hrs	4 (1.2%)	260 (76.9%)	47 (13.9%)	16 (4.7%)	6 (1.8%)	3 (0.9%)	1 (0.3%)	1 (0.3%)	0	0
		168 Hrs	3 (0.9%)	249 (73.7%)	55 (16.3%)	18 (5.3%)	6 (1.8%)	3 (0.9%)	3 (0.9%)	0	1 (0.3%)	0

Abbreviations: Corplex Donepezil TDS = 53.5 cm^2 TDS (donepezil 5 mg/day) lead-in during Week 1 followed by 107 cm^2 TDS (donepezil 10 mg/day) during Weeks 2 to 5; N = number of subjects with patches in the adhesion population; n = number of patches in the adhesion population; TDS = transdermal delivery system; TDS Appl = adhesion score at the time of TDS application.

Note: Percentages were calculated as the number of patches with a given adhesion score at each time point divided by n and multiplied by 100.

a. Adhesion score (percent adhered): 0 = 100%; 1 = 90% to < 100%; 2 = 80% to < 90%; 3 = 70% to < 80%; 4 = 60% to < 70%; 5 = 50% to < 60%; 6 = 40% to < 50%; 7 = 30% to < 40%; 8 = 20% to < 30%; 9 = 10% to < 20%; 10 = > 0% to < 10%; 11 = complete detachment. The adhesion score at a post application time point for a given TDS was the highest post application score observed at or prior to the time point.

b. Includes all patches in the adhesion population applied during Weeks 2 to 5 combined.

Source: Section 14.3.9.1.1.

The applicant concludes the mean adhesion score analysis demonstrated that the average adherence exceeded 90%. Further, only about 1.2% of the Donepezil TDS [10 mg/day]) had less than 50% adhesion at any time point during the wear period with the mean time to the first occurrence of less than 50% adhesion for the whole TDS being 5.9 days. Adhesion of the drug delivery area was greater than that of the whole TDS (i.e. adhesion scores tended to be lower), (b) (4)

P-16012

For the back location, an ad-hoc analysis showed 83.1% of all TDS applied (49 of 59) were at least 90% adhered and 91.6% (54 of 59) were at least 80% adhered through hour 168. One subject (1.7%) was less than 50% adhered by 84 hours. This subject was removed from analysis on study Day 4 due to lack of adhesion, however a score of 11 (0% adhered) was assigned to all subsequent time points through Hour 168. Notable this subject had all scores of 0 or 1 (90-100%) for all timepoints at other treatment sites (thigh and buttock).

For the thigh location, an ad-hoc analysis (performed because two subjects self-taped) showed 80.3% (49 of 61) were at least 90% adhered and 95.1% (58 of 61) were at least 80% adhered through hour 168. The applicant noted removal of the two subjects minimally altered the percentages. One TDS (1.6%) applied to the thigh was less than 50% adhered with a mean time to first occurrence at 3.99 days. No products applied to the thigh detached.

For the buttock location, an ad-hoc analysis indicated 98.4% (61 of 62) of TDS applied were at least 90% adhered and 100% were at least 80% adhered through the end of the wear period.

Table 23: Adhesion Score Frequency Summary for the Whole Corplex Donepezil TDS Area (Study P-16012, Adhesion Population)

Complex TDS Application Site Number of Corplex Donepezil TDS (n)	Hours Post-Corplex Donepezil TDS Application	Corplex Donepezil TDS Whole Patch Adhesion Score (N = 66)											
		0	1	2	3	4	5	6	7	8	9	10	11
Back (n = 60)	12 Hrs	35 (58.3%)	25 (41.7%)	0	0	0	0	0	0	0	0	0	0
	24 Hrs	33 (55.0%)	27 (45.0%)	0	0	0	0	0	0	0	0	0	0
	36 Hrs	21 (35.0%)	38 (63.3%)	0	1 (1.7%)	0	0	0	0	0	0	0	0
	48 Hrs	19 (31.7%)	39 (65.0%)	1 (1.7%)	1 (1.7%)	0	0	0	0	0	0	0	0
	60 Hrs	15 (25.0%)	38 (63.3%)	5 (8.3%)	1 (1.7%)	1 (1.7%)	0	0	0	0	0	0	0
	72 Hrs	10 (16.7%)	43 (71.7%)	4 (6.7%)	2 (3.3%)	0	1 (1.7%)	0	0	0	0	0	0
	84 Hrs	6 (10.0%)	46 (76.7%)	5 (8.3%)	2 (3.3%)	0	0	0	0	1 (1.7%)	0	0	0
	96 Hrs	5 (8.3%)	46 (76.7%)	6 (10.0%)	1 (1.7%)	1 (1.7%)	0	0	0	0	0	0	1 (1.7%)
	108 Hrs	3 (5.0%)	46 (76.7%)	7 (11.7%)	1 (1.7%)	1 (1.7%)	1 (1.7%)	0	0	0	0	0	1 (1.7%)
	120 Hrs	3 (5.0%)	44 (73.3%)	9 (15.0%)	1 (1.7%)	1 (1.7%)	1 (1.7%)	0	0	0	0	0	1 (1.7%)
	132 Hrs	1 (1.7%)	46 (76.7%)	9 (15.0%)	1 (1.7%)	1 (1.7%)	1 (1.7%)	0	0	0	0	0	1 (1.7%)
	144 Hrs	0	47 (78.3%)	8 (13.3%)	2 (3.3%)	1 (1.7%)	1 (1.7%)	0	0	0	0	0	1 (1.7%)
	156 Hrs	0	46 (76.7%)	9 (15.0%)	2 (3.3%)	1 (1.7%)	1 (1.7%)	0	0	0	0	0	1 (1.7%)
	168 Hrs	0	41 (68.3%)	10 (16.7%)	5 (8.3%)	2 (3.3%)	1 (1.7%)	0	0	0	0	0	1 (1.7%)
Thigh (n = 61)	12 Hrs	52 (85.2%)	9 (14.8%)	0	0	0	0	0	0	0	0	0	0
	24 Hrs	47 (77.0%)	14 (23.0%)	0	0	0	0	0	0	0	0	0	0
	36 Hrs	42 (68.9%)	18 (29.5%)	1 (1.6%)	0	0	0	0	0	0	0	0	0
	48 Hrs	39 (63.9%)	21 (34.4%)	1(1.6%)	0	0	0	0	0	0	0	0	0
	60 Hrs	33 (54.1%)	26 (42.6%)	2 (3.3%)	0	0	0	0	0	0	0	0	0
	72 Hrs	28 (45.9%)	31 (50.8%)	2 (3.3%)	0	0	0	0	0	0	0	0	0
	84 Hrs	25 (41.0%)	34 (55.7%)	2 (3.3%)	0	0	0	0	0	0	0	0	0
	96 Hrs	18 (29.5%)	40 (65.6%)	2 (3.3%)	0	0	0	0	0	0	0	1 (1.6%)	0
	108 Hrs	16 (26.2%)	41 (67.2%)	3 (4.9%)	0	0	0	0	0	0	0	1 (1.6%)	0
	120 Hrs	13 (21.3%)	44 (72.1%)	3 (4.9%)	0	0	0	0	0	0	0	1 (1.6%)	0
	132 Hrs	10 (16.4%)	44 (72.1%)	5 (8.2%)	0	1 (1.6%)	0	0	0	0	0	1 (1.6%)	0
	144 Hrs	10 (16.4%)	43 (70.5%)	6 (9.8%)	0	1 (1.6%)	0	0	0	0	0	1 (1.6%)	0
	156 Hrs	9 (14.8%)	43 (70.5%)	6 (9.8%)	1 (1.6%)	1 (1.6%)	0	0	0	0	0	1 (1.6%)	0
	168 Hrs	5 (8.2%)	44 (72.1%)	9 (14.8%)	1 (1.6%)	1 (1.6%)	0	0	0	0	0	1 (1.6%)	0

Complex TDS Application Site Number of Corplex Donepezil TDS (n)	Hours Post-Corplex Donepezil TDS Application	Corplex Donepezil TDS Whole Patch Adhesion Score (N = 66)											
		0	1	2	3	4	5	6	7	8	9	10	11
Buttock (n = 62)	12 Hrs	45 (72.6%)	17 (27.4%)	0	0	0	0	0	0	0	0	0	0
	24 Hrs	38 (61.3%)	24 (38.7%)	0	0	0	0	0	0	0	0	0	0
	36 Hrs	36 (58.1%)	26 (41.9%)	0	0	0	0	0	0	0	0	0	0
	48 Hrs	31 (50.0%)	31 (50.0%)	0	0	0	0	0	0	0	0	0	0
	60 Hrs	30 (48.4%)	32 (51.6%)	0	0	0	0	0	0	0	0	0	0
	72 Hrs	24 (38.7%)	38 (61.3%)	0	0	0	0	0	0	0	0	0	0
	84 Hrs	23 (37.1%)	39 (62.9%)	0	0	0	0	0	0	0	0	0	0
	96 Hrs	20 (32.3%)	42 (67.7%)	0	0	0	0	0	0	0	0	0	0
	108 Hrs	19 (30.6%)	43 (69.4%)	0	0	0	0	0	0	0	0	0	0
	120 Hrs	18 (29.0%)	44 (71.0%)	0	0	0	0	0	0	0	0	0	0
	132 Hrs	15 (24.2%)	47 (75.8%)	0	0	0	0	0	0	0	0	0	0
	144 Hrs	12 (19.4%)	49 (79.0%)	1 (1.6%)	0	0	0	0	0	0	0	0	0
	156 Hrs	11 (17.7%)	49 (79.0%)	2 (3.2%)	0	0	0	0	0	0	0	0	0
	168 Hrs	9 (14.5%)	51 (82.3%)	2 (3.2%)	0	0	0	0	0	0	0	0	0

Abbreviations: Corplex Donepezil TDS = 10 mg/day Donepezil (1 × 107 cm^2 Corplex Donepezil TDS) applied at Hour 0 on Day 1 for 7 days; N = number of subjects with Corplex Donepezil TDS in the adhesion population in each application site; n = number of Corplex Donepezil TDS in the adhesion population per application site; TDS = transdermal delivery system.

Note: Adhesion Score: 0 = 100% adhered; 1 = 90% to < 100% adhered; 2 = 80% to < 90% adhered; 3 = 70% to < 80% adhered; 4 = 60% to < 70% adhered; 5 = 50% to < 60% adhered; 6 = 40% to < 50% adhered; 7 = 30% to < 40% adhered; 8 = 20% to < 30% adhered; 9 = 10% to < 20% adhered; 10 = > 0% to < 10% adhered; 11 = detached. The adhesion score at a post application time point for a given Corplex Donepezil TDS is the highest post application score observed at or prior to the time point. If a Corplex Donepezil TDS became completely detached before the end of the 7-day Corplex Donepezil TDS wear period, a score of 11 (complete Corplex Donepezil TDS detachment) was carried forward for all subsequent Corplex Donepezil TDS assessments.

Note: Percentages are calculated based on the number of Corplex Donepezil

Note: For Subject (b) (6), the Corplex Donepezil TDS placed on the TDS Back was removed on Study Day 4 of Treatment Period 1 due to lack of adhesion; the adhesion score entered in the database after this point was 11 = completely detached.

Source: Table 14.3.9.1.1

The applicant concludes a favorable adhesion profile was demonstrated at all three sites based on mean score analysis and that all three locations demonstrated approximately 90% or better surface area adhesion for the majority of systems applied. Only one TDS in total became completely detached (site location was the Back).

Reviewer's Assessment:

Traditionally, mean adhesion score is utilized in a non-inferiority study, such as adhesion studies conducted for ANDA products.[1] The Applicant also provided ad-hoc analysis and frequency tables showing point by point % adhesion for all products applied. The applicant's analysis indicated that more than 80% of all products applied (5 mg and 10 mg/day) and to all application sites (back, thigh, buttock) maintain at least 80% of surface area adherence throughout the duration of wear. Slight difference were noted between sizes and application sites but none that would be deemed a negative trend related to adhesion. Only one complete detachment (on the back) was reported and relatively few with <50% surface area adherence. A random sampling (chosen by the reviewer) of photographs of subjects from P-16010 were provided which verified scoring was appropriate. The applicant also emphasized that when detachment is seen it is most often (b) (4)

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[1] *Draft Guidance for Industry: Assessing Adhesion with Transdermal Delivery Systems and Topical Systems for ANDAs*
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM504157.pdf

Office of Biostatistics Assessment

A statistical consult was requested by the Office of Pharmaceutical Quality to assess the *in vivo* adhesion data for NDA 212304. The Office of Biostatistics evaluated data from Studies P-15086, P-16007, P-16010, and P-16012. Refer to the Biostatistics Consult response dated 20-MAY-2020 for full details.

In summary:

Overall, the data from all studies support that the probability of a TDS maintaining at least 80% surface area adhesion during the entire wear period for the 10 mg/day donepezil is at least 80% (95% lower confidence limit was achieved in all studies except for P-16007, likely due to small sample size).

The statistical hypothesis test used in evaluation was as follows:

Let p denote the probability that a randomly selected TDS maintains at least 80% of a TDS's total surface area adhesion during its entire wear period. p is estimated by the proportion of TDS in the wear study that maintain a surface area adhesion of at least 80% at every timepoint.

- $H_0: p \leq p_0$ versus $H_1: p > p_0$.
- p_0 should be set at no less than 0.80.

- H_0 is rejected if the 95% lower confidence limit of p is greater than p_0 .

In the summary tables below, "Sample Size" represents the number of systems applied, and "Count" represents the number of TDS applied that maintained at least 80% adhesion for the duration of wear, the Jeffery's and SOC Confidence Limits are also shown.

For study P-16012 the following summary was obtained:

Treatment	Dosage	Sample size	Count	Point estimate	Jeffreys CL	SOC CL
Donepezil TDS	5	85	80	0.94	0.89	0.89
Donepezil TDS	10	338	307	0.91	0.88	0.88

Table 3: Summary of the point estimate and 95% lower confidence limits of the probability that a TDS maintains at least 80% adhesion during the entire wear period for both strengths (5 mg/day donepezil (1 × 53.5 cm^2 Corplex Donepezil TDS) (Lot Number: 38090) and Target dose of 10 mg/day donepezil (1 × 107 cm^2 Corplex Donepezil TDS) (Lot Number: 38090B)) for Study P-16010.

For study P-16010 the following summary was obtained:

Site	Sample size	Count	Point estimate	Jeffreys CL	SOC CL
Back	60	51	0.85	0.76	0.76
Buttock	62	62	1.00	0.97	0.97
Thigh	61	58	0.95	0.89	0.89
All	183	171	0.93	0.90	0.90

Table 5: Summary of the point estimate and 95% lower confidence limits of the probability that a TDS maintains at least 80% adhesion during the entire wear period for Target dose of 10 mg/day donepezil (1 × 107 cm^2 Corplex Donepezil TDS) (Lot Number: 38090B) for each week for Study P-16012.

Office of Biostatistics Conclusion: P-16010 and P-16012 support that the probability of a TDS maintaining at least 80% surface area adhesion during the entire wear period of the largest size product is at least 80% (with the majority of the applications being on the back in these studies). The results of P-16012 indicate that adhesion is the greatest on the buttock, followed by the thigh and then the back.

Quality of the Product

The quality control methods of the drug product release and stability specification (adhesion, tack, peel from release liner, shear and cold flow) are used to ensure the adhesive character of the TDS is consistent batch to batch and throughout its shelf life. Although the majority of these tests do not correlate to in vivo adhesion performance, when tests and acceptance criteria are appropriately establish they do provide a level of quality assurance of current and future batches. Ultimately the goal of quality adhesion testing is to assure that future batches are comparable to those batches which were tested and exhibited adequate *in vivo* adhesion. Per the OPQ Drug Product Review, the applicant has established an adequate specification with respect to the adhesion, peel from release liner, shear, tack and cold flow. However, as noted above separation of the layers is a significant quality issue. Early in the review cycle the applicant

was requested to develop a method for the separation strength of (b) (4) . In a response to an information request dated 28-Feb-2020, the Applicant provided details regarding the newly developed method. However, a response providing the acceptance criteria and justification has yet to be submitted. Additionally, and within the review cycle, the Applicant proposed multiple changes to the manufacturing process and it is unclear if the currently proposed product is equivalent to that used in the clinical trial which assessed adhesion. Depending on how the deficiencies of the CR letter are addressed by the applicant for a resubmission, a new adhesion study may be necessary as well as a re-evaluation of the established acceptance criteria. Refer to the OPQ Drug Product Review for more information.

Life Cycle Consideration

As alluded to in the Background section of this review, a significant quality issue related to separation (b) (4) was identified. Although the applicant has proposed labeling changes and minor physical changes to the product (such as (b) (4)) during this review cycle, the significant quality issue remains unmitigated as of the date of this review. It is unclear at this time how the applicant will adequately address this issue in a future resubmission (e.g. (b) (4)) therefore, depending on the changes made to the product, a new adhesion study may or may not be required.

Labeling Language

The below language should be incorporated into section 14 of the PI. If new studies are conducted in the resubmission the below information should be modified to accommodate the new studies.

Based on a clinical study in 85 subjects, each wearing one ADLARITY 5 mg/24 hours on the back, 80 transdermal systems (94%) exhibited 80% or greater surface area adhesion at all timepoints evaluated (every 12 hours) throughout the 168 hour wear period. Based on a clinical study in 85 subjects, each wearing an ADLARITY 10 mg/24 hours for 168 hours on the back for 4 consecutive weeks, 307 of 338 transdermal systems (91%) exhibited 80% or greater surface area adhesion at all timepoints evaluated. No full detachments were seen for any TDS applied. In a separate study which assessed wear at different application sites (back, thigh, and buttock) at least 85% of the TDS applied at every site exhibited (b) (4) 80% adhesion for the duration of wear. One full detachment on the back was noted in the study.

Overall Recommendation:

From a quality perspective, the formulation of the drug product used in clinical study P-16010 and P-16012 demonstrates ADEQUATE in vivo adhesion for the prescribed 7-day wear period. Although the size of the active area differed slightly (<2%) in these studies, the overall size remained the same and no significant or negative impact related to adhesion is expected for the proposed commercial product.

The applicant has demonstrated that the probability that at least 80% of all ADLARITY TDS will maintain at least 80% surface area adhesion during the entire wear period using both the largest and smallest sizes and for all application sites (back, buttock, and thigh).

The quality recommendation for adhesion to the Office of New Drugs of ADLARITY (donepezil) transdermal system is APPROVABLE.

Note, if significant changes to the product are made to address the Complete Response issues and a new adhesion study is necessitated, a new assessment of that data and new recommendation for adhesion will be required.

Caroline Strasinger, Ph.D.
OPQ/ONDP/ DNDP II
Chair, Transdermal Drug Working Group
28-MAY-2020

17 Page(s) have been Withheld in Full immediately following this page - 4 pages as b4 (CCI/TS) and 13 pages as duplicative of the Statistical review dated 5/20/2020 that appears in the Statistical Review

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/s/

CAROLINE STRASINGER
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