CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212304Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW

Date	March 9, 2022
From	Ranjit B. Mani, MD Teresa J. Buracchio, MD
Division/Office	Division of Neurology 1 Office of Neuroscience
Subject	Summary Review (Cross-Disciplinary Team Leader Review)
NDA/BLA # Supplement#	NDA 212304 Class 2 Resubmission
Applicant	Corium, Inc.
Date of Submission	September 13, 2021
PDUFA Goal Date	March 13, 2022
Proprietary Name / Established (USAN) names	ADLARITY (Donepezil Transdermal System)
Dosage forms / Strength	5 mg/day 10 mg/day
Proposed Indication(s)	Treatment of mild, moderate, and severe dementia of the Alzheimer's type
Action:	Approval

1. Background

This submission, a Class 2 Resubmission, responds to an Agency Complete Response letter dated July 23, 2020.

The Complete Response letter was, in turn, directed at a New Drug Application (NDA) seeking the approval of ADLARITY (donepezil transdermal system) for the treatment of mild, moderate, and severe dementia of the Alzheimer's type. That NDA was submitted on September 29, 2019: the application was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, relying in part on the Agency's prior findings of safety and effectiveness for ARICEPT (donepezil) tablets in the treatment of Alzheimer's disease, under NDA 20690.

Donepezil is currently marketed in this country under the brand name ARICEPT [Eisai] as a tablet in 5 mg, 10 mg, and 23 mg strengths; their approval has been under NDA 20690 and NDA 22568. The 5 mg and 10 mg strengths of ARICEPT have been approved for the treatment of mild to moderate dementia of the Alzheimer's type. The 10 mg and 23 mg strengths of the tablet formulation have additionally been approved for the treatment of moderate to severe dementia of the Alzheimer's type. Orally-disintegrating tablets of ARICEPT, of 5 mg and 10 mg strength were previously marketed in this country. Generic tablet formulations of donepezil of 5 mg and 10 mg strength are also marketed in this country.

Under the current application, it is proposed that ADLARITY be administered once weekly. As already noted, oral formulations of donepezil, including those of ARICEPT, are administered once daily.

The development of ADLARITY for the proposed indication has been conducted under Investigational New Drug Application (IND) 129778. During this development program, the ADLARITY transdermal delivery system has earlier been referred to as the Corplex™ Donepezil Transdermal Delivery System.

2. Outline Of Original NDA Submission

As already noted, this NDA was initially submitted on September 29, 2019, in response to which an Agency Complete Response letter was issued on July 23, 2020. As also noted, this NDA was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, relying in part on the Agency's prior findings of safety and effectiveness for ARICEPT (donepezil) tablets in the treatment of Alzheimer's disease, under NDA 20690.

Please see Agency reviews of the contents of this application for further details. These reviews included a Cross-Disciplinary Team Leader review (summary memorandum).

2.1 Contents Of Original NDA Submission

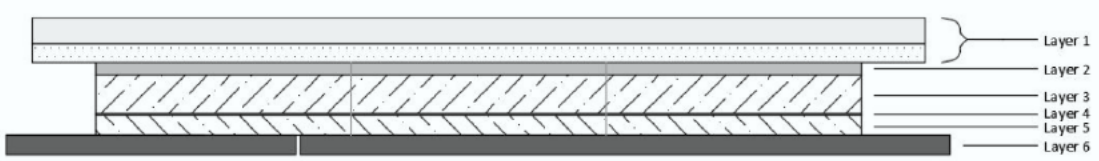
Several of the key components of that application are summarized below. More extensive data supporting each component of the application were of course included in that application.

2.1.1 Description And Composition Of ADLARITY Transdermal System

Each ADLARITY transdermal delivery system was intended to continuously deliver donepezil in a dose of either 5 mg/day or 10 mg/day for 7 days. The systems delivering 5 mg/day and 10 mg/day were to measure 52.5 cm^2 and 105 cm^2, respectively.

Each ADLARITY transdermal delivery system was to consist of a rectangular 6-layer matrix-type patch with the following layers: an overlay backing/adhesive layer (tan colored); a separating layer; a drug matrix layer; a microporous membrane layer; a skin contact adhesive layer; and a peel-off blue-tinted release liner.

A cross-sectional schematic (not-to-scale) view of the proposed ADLARITY transdermal delivery system is displayed in the sponsor figure below.



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)

2.1.2 List Of Clinical Studies Conducted In Support Of Application

A full list of the clinical studies conducted in support of original submission of this NDA is in the following sponsor table.

Study Number	Study Title	Brief Objectives
P-15007	A Phase 1, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Two Formulations of a 7-Day Application of Donepezil Transdermal Delivery System Compared to Oral Administration of Aricept in Healthy Volunteers	Assess initial TDS formulation performance
P-15081	A Phase 1 Parallel Study to Evaluate the Pharmacokinetics (PK), Pharmacodynamics (PD) and Safety of Formulations of a 7-Day Application Donepezil Transdermal Delivery System (TDS) in Healthy Female Volunteers	Formulation Selection
P-16007	A Phase 1 Study to Evaluate the Adhesion, Pharmacokinetics (PK) and Safety of a Seven-Day Application of Donepezil Transdermal Delivery System (TDS) in Healthy Volunteers	Adhesion Optimization
P-15086	A Phase 1, Randomized, Open-Label, 3-Way Crossover, Pilot, Pharmacokinetic Study to Evaluate the Steady State Pharmacokinetics of a Once-Weekly Application of Corplex™ Donepezil Transdermal Delivery System Compared to Daily Oral Administration of Aricept® in Healthy Adult Subjects	Steady state Bioequivalence
P-16011	A Randomized Double-Blind Study to Assess the Skin Irritation and Sensitization Potential of Once-Weekly Corplex™ Donepezil Transdermal Delivery System	Skin Irritation/ Sensitization
P-16012	A Phase 1, Crossover Study to Evaluate the Pharmacokinetics of Corplex™ Donepezil 10 mg Transdermal Delivery System Applied to Different Body Locations	Relative Bioavailability - Application Site (back, thigh, buttock)
P-16039	A Phase 1, 2-Way Crossover Study to Evaluate the Effect of Heat Application on the Pharmacokinetics of Corplex™ Donepezil 5 mg Transdermal Delivery System (TDS) in Healthy Volunteers	Relative Bioavailability – Applied Heat
P-16010	A Study to Assess the Steady State Bioequivalence of Once-Weekly Corplex™ Donepezil 10 mg Transdermal Delivery System Compared to Daily Oral Administration of Aricept®	Safety/Tolerability and Adhesion
P-15086 Sub-Study*	A Phase 1, Randomized, Open-Label, 2-Way Crossover Study, to Compare the Relative Bioavailability of Two Corplex Donepezil Trandsdermal Delivery Systems' Manufactured Using Active Pharmaceutical Ingredient from two Different Suppliers	Relative Bioavailability - API Supplier

**The P-15086 Sub-Study was conducted as an amendment to Protocol No. P-15086.*

2.2 Discipline Reviews Of Original NDA

The contents of the individual discipline reviews of the original NDA are summarized below.

2.2.1 Integrated Quality Review

A serious product quality deficiency was noted during the review of this application: (b) (4) layers could be separated by hand, or even by removing the release liner. As a result, an increased risk of the following had been identified:

- Unintentional overdose.

- Under-dosing and ineffective treatment.
- Potential misuse.
- Accidental exposure to donepezil (for those other than the patient).

Attempts to correct this deficiency during the course of this review, through multiple communications with the sponsor, had been unsuccessful.

Other product quality deficiencies with this application had also been identified.

The review team for that discipline had concluded that:

- The sponsor had not provided sufficient Chemistry, Manufacturing, and Controls information to assure the identity, strength, purity, and quality of the drug product.
- The deficiencies in the application precluded labeling discussions and the completion of a labeling review (by the same review team).

This review team had, primarily for the above reasons, recommended that a Complete Response letter be issued for this application.

2.2.1.1 Biometrics Review Of In Vivo Adhesion Data

This review had concluded that the probability of an ADLARITY transdermal system maintaining adhesion was at least 75% for the entire wear period. The review further stated that the available data suggested that adhesion is best when that transdermal system is applied to the back, with less adhesion when that system is applied to the thigh, and even less adhesion when that system is applied to the buttock.

2.2.2 Clinical Review

Among the main observations of the clinical reviewer were the following:

- The safety and tolerability of ADLARITY were satisfactory, extending to low skin irritation and sensitization, and to gastrointestinal, central nervous system, and other systemic adverse events.
- No clinical efficacy studies of ADLARITY were conducted, as bioequivalence has been demonstrated between that product and ARICEPT tablets.

2.2.3 Clinical Pharmacology Review

This review team had noted that bioequivalence was established at steady state between the ADLARITY once-weekly transdermal system and ARICEPT in the pivotal clinical pharmacology study P-15086, for both C_{max} and $AUC_{0\text{-}tau}$.

This review team had also noted that the manufacturing process used for the ADLARITY transdermal system product investigated in Study P-15086 was not the same as that proposed for the ADLARITY commercial product. Thus, further pharmacokinetic data were needed to bridge the product used in pivotal study P-15086 and the commercial ADLARITY product.

This review team had concluded that the information submitted in support of this application was not acceptable. The same review team had also stated that discussions of labeling were therefore premature.

2.2.4 Nonclinical Review

The results of the special local toxicity studies of ADLARITY were reviewed.

The reviewer had concluded that the nonclinical data submitted with this application adequately supported the approval of ADLARITY for the treatment of patients with Alzheimer's disease.

2.2.5 Labeling Comprehension Study Report Review

This review addressed the results of the sponsor's Human Factors Labeling Comprehension Study evaluating the clarity and effectiveness of the labeling instructions for application, removal and disposal of the ADLARITY transdermal system.

On account of multiple deficiencies, the reviewer was unable to conclude that sponsor's Human Factors Labeling Comprehension Study confirmed patients' and caregivers' understanding of the safe and effective application, removal, and disposal of the proposed ADLARITY transdermal system.

2.2.6 Label, Labeling, And Packaging Review

A number of recommendations were made in this review regarding the contents of the Prescribing Information and the packaging for this product.

2.2.7 Proprietary Name Review

This review had concluded that the proprietary name ADLARITY was acceptable for this product.

2.3 Agency Conclusion

The sponsor had not provided sufficient information in the original NDA to support the approval of ADLARITY (donepezil transdermal system) for the treatment of mild, moderate, and severe Alzheimer's disease.

The salient deficiencies in this application were:

- A product quality defect: a failure of key layers in the ADLARITY transdermal system (b) (4).

- A lack of pharmacokinetic data that might bridge the commercial ADLARITY formulation with that used in the pivotal bioequivalence study P-15086.

A Complete Response letter was therefore issued for this application.

2.4 Complete Response Letter: July 23, 2020

A Complete Response letter was issued for this application on July 23, 2020. The full text of that letter is attached. That text is self-explanatory.

3. Communications Between Agency And Sponsor Following Issuance Of Complete Response Letter.

There were a number of communications between the Agency and sponsor following the Agency's issuance of the Complete Response letter of July 23, 2020.

These included, but were not limited to, a Type A meeting (teleconference) between the Agency and sponsor that was held on October 13, 2020. Please see the minutes of that meeting (attached) for further details.

4. Description And Composition Of Current ADLARITY Transdermal System

Each ADLARITY transdermal delivery system is intended to continuously deliver donepezil in a dose of either 5 mg/day or 10 mg/day for 7 days.

Each ADLARITY transdermal delivery system is a rectangular 6-layer matrix-type patch with the following layers: an overlay backing/adhesive layer (Layer 1); a separating layer (Layer 2); a drug matrix layer (Layer 3); a microporous membrane layer (Layer 4); a skin contact adhesive layer (Layer 5); and a peel-off blue-tinted release liner (Layer 6)

The structure of each ADLARITY transdermal delivery system is displayed in the following graphic (a cross-sectional view that is not to scale) which I have copied from the submission.

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)

The systems delivering 5 mg/day and 10 mg/day measure 52.5 cm^2 and 105 cm^2, respectively, in their active delivery area.

5. List Of Additional Clinical Studies Conducted In Support Of This Application

The additional clinical studies included in this Resubmission in support of the current application are displayed in the sponsor table below.

Study Number	Study Title	Brief Objectives
CL-P-20003	A Phase 1, Open-Label, 3-Period, Randomized, Crossover Pharmacokinetic Study to Evaluate the Steady-State Pharmacokinetics of 5 mg and 10 mg Corplex™ Donepezil Transdermal Delivery Systems Compared to 10 mg Oral Administration of Aricept® in Healthy Volunteers	Relative Bioavailability – Final TDS vs RLD [a]
CL-P-20004	A Phase 1, Open-Label, Randomized, 2-Period, Crossover Pharmacokinetic Study Comparing Two Corplex Donepezil Transdermal Delivery Systems of Different Age in Healthy Volunteers	Relative Bioavailability/Shelf-life Support – TDS of Different Age
P-16010 [b]	A Study to Assess the Steady State Bioequivalence of Once-Weekly Corplex™ Donepezil 10 mg Transdermal Delivery System Compared to Daily Oral Administration of Aricept®	Relative Bioavailability/ Formulation Bridging – (b) (4) TDS vs RLD
CL-P-19005	A Phase 1, Randomized, Blinded, 2-Way Crossover Study to Assess the Relative Bioavailability of Corplex™ Donepezil Transdermal Delivery Systems With and Without Crystals	Relative Bioavailability – TDS With vs Without Crystals

a. RLD = Reference Listed Drug: Aricept® tablets for oral administration.
b. The safety/tolerability and adhesion results of Study P-16010 were included in the original NDA.

The reports of Studies CL-P-20003, CL-P-20004, and CL-P-19005 are entirely new, i.e., no elements of those reports were included in the original submission of this NDA. However, as a footnote to this table indicates, the safety and skin adhesion data for Study P-16010 were included in the original NDA (they were fully reviewed by the Agency at that time).

6. Discipline Reviews Of Resubmission

The contents of the individual discipline reviews of this application are summarized below.

6.1 Integrated Quality Review

The Integrated Quality Review of this application Resubmission was completed by the following primary reviewers: Drs. Andrei Ponta, Youmin Wang, and Kaushalkumar Dave. Several secondary reviewers and other reviewer staff are also listed. The Application Technical Leads were Drs. Caroline Strasinger and Martha Heimann. This review was fully completed and signed on March 7, 2022.

As already noted in this review, a serious product quality deficiency was noted in the drug product during the review of the original submission under this application: (b) (4) layers could be separated by hand, or even by removing the release liner. As a result, an increased risk of the following had been identified: unintentional overdose; under-dosing and ineffective treatment; potential misuse; and accidental exposure to donepezil (for those other than the patient).

As described in the current submission, the sponsor has addressed the above deficiency by (b) (4) Additional testing has confirmed the effectiveness (b) (4) in preventing the separation (b) (4).

The following additional deficiencies that were noted during review of the original submission of this NDA have also been addressed satisfactorily in this Resubmission: changes during long-term storage; (b) (4); pouch seal strength; shelf-life; crystal inspection; outstanding information requests; and other items.

Based on the above, the Agency's Integrated Quality Review team has concluded that the outstanding deficiencies in quality described in the Agency's Complete Response letter of July 23, 2020, have been adequately addressed. That team has therefore recommended the approval of this application.

6.2 Clinical Pharmacology Review

The Office of Clinical Pharmacology review team consisted of Drs. Min Li, Vishnu Sharma, Atul Bhattaram, and Bilal AbuAsal. This review was fully completed and signed on March 7, 2022.

Their main observation was based on Study CL-P-20003.Study CL-P-20003 was a new pivotal relative bioavailability study that was intended to compare the steady state donepezil pharmacokinetics of the to-be-marketed (b) (4) ADLARITY transdermal delivery system delivering 5 mg/day and 10 mg/day, with ARICEPT 10 mg tablets. The results of this study confirmed that the geometric mean ratios for the C_{max} and $AUC_{0\text{-}tau}$ met the bioequivalence criteria for both strengths of the ADLARITY transdermal delivery system. In addition, the C_{trough} for ADLARITY was not inferior to that of ARICEPT and the two strengths of the ADLARITY transdermal delivery system were dose proportional based on a bioequivalence analysis. The concentrations of the active metabolite of donepezil (6-O-desmethyl-donepezil) were very low relative to

donepezil exposure and any differences in exposure to that metabolite between the ADLARITY transdermal delivery system (delivering 5 mg/day and 10 mg/day), and ARICEPT 10 mg tablets was considered clinically insignificant.

The review team also briefly reviewed the results of the following studies, in all three of which evidence of bioequivalence was demonstrated between the studied treatments.

- Study CL-P-20004 which compared the relative bioavailability of (b) (4) ADLARITY transdermal delivery system (5 mg/day) stored for about 24 months at 2-8 degrees C with the pharmacokinetics of (b) (4) ADLARITY transdermal delivery system (5 mg/day) stored for about 24 months at 2-8 degrees C.

- Study CL-P-19005 which compared the relative bioavailability of the ADLARITY transdermal delivery system (10 mg/day) without crystals with the ADLARITY transdermal delivery system (10 mg/day) with crystals ((b) (4) ADLARITY transdermal delivery system was investigated in this study).

- Study CL-P-16010, for which data included in this submission compared the pharmacokinetics of (b) (4) ADLARITY transdermal delivery system (10 mg/day) with ARICEPT 10 mg QD.

This team has also conducted pharmacokinetic simulations to determine the most appropriate regimen for transitioning from oral ARICEPT (5 mg/day and 10 mg/day) to the ADLARITY transdermal delivery system. The results of those simulations, which are summarized in the clinical pharmacology review, have also been discussed with the clinical team reviewing this application. Based on that discussion, it has been concluded that the first dose of the ADLARITY transdermal delivery system should be applied at the same time as the last dose (of the equivalent dose) of ARICEPT is taken. That recommendation has been included in the Prescribing Information for the ADLARITY transdermal delivery system.

Based on the above, the clinical pharmacology team has therefore recommended the approval of this application.

6.3 Clinical Review

Brian Trummer, MD, PhD, was the clinical reviewer of this application. His review was completed on March 9, 2022.

His review has focused on the clinical safety and tolerability data for Studies CL-P-20003, CL-P-20004, and CL-P-19005.

His review indicates, that, as with the clinical safety data included in the original submission of this NDA, the safety and tolerability of ADLARITY (as demonstrated by the data included in the current submission) were satisfactory, extending to low skin irritation

and sensitization, and to gastrointestinal, central nervous system, and other systemic adverse events. No new clinical safety concerns emerged as a result of his review.

Dr. Trummer has recommended that this application be approved.

6.4 Label, Labeling, And Packaging Review

This review was completed on February 10, 2022, by Chad Morris, PharmD, MPH, of the Division of Medical Error Prevention and Analysis 2.

Dr. Morris has noted that the Agency's recommendations made by the same team during the review of the original NDA submission for ADLARITY have been accepted. There are no new recommendations in his review.

6.5 Office Of Prescription Drug Promotion Review

This review was completed on February 25, 2022, by Rebecca Falter, PharmD, BCACP of the Office of Prescription Drug Promotion.

The following components of this Resubmission were reviewed by that Office: Prescribing Information; Patient Package Insert; Instructions for Use; and Carton and Container Labeling.

Comments were provided in this review regarding the following items from the above list: Prescribing Information; and Carton and Container Labeling. These comments were then considered further by this Division.

Comments regarding the Patient Package Insert and Instructions for Use were provided in a separate Patient Labeling Review (see below).

6.6 Patient Labeling Review

This review was completed on February 24, 2022, by Mary Carroll, BSN, RN, of the Division of Medical Policy Programs, and Rebecca Falter, PharmD, BCACP of the Office of Prescription Drug Promotion.

This review focused on the Patient Package Insert and Instructions for Use. The draft Prescribing Information for ADLARITY and the approved Prescribing Information for ARICEPT were also referenced during this review.

The two reviewers recommended changes to both the Patient Package Insert and Instructions for Use. These comments were then considered further by the Division

6.7 Bioestablishment Inspection Report

The Bioestablishment Inspection Report for this application was completed by Nicola Fenty-Stewart of the Division of New Study Integrity, Office of Study Integrity and Surveillance, on February 18, 2022.

This report states that the Division of New Study Integrity of the Office of Study Integrity and Surveillance determined that an on-site inspection was not warranted for the following study site in relation to this application: Worldwide Clinical Trials (WCT) Early Phase Services, LLC, 2455 Northeast Loop 410, Suite 150, San Antonio, TX 78217. The rationale for that determination was that the same site had been inspected in October 2018 in regard to three Abbreviated New Drug Applications (ANDAs) and the final classification of that inspection was “Voluntary Action Indicated,”

7. Conclusion And Recommendation

Under NDA 212304, submitted on September 29, 2019, the applicant had sought the approval of ADLARITY (donepezil transdermal system) for the treatment of mild, moderate, and severe dementia of the Alzheimer’s type. On account of chemistry and clinical pharmacology deficiencies in that application, the Agency responded with a Complete Response letter dated July 23, 2021.

In the current Class 2 Resubmission of NDA 212304, the applicant has adequately addressed the deficiencies in the original application.

This application may therefore be approved, using labeling agreed to between the Agency and sponsor.

Ranjit B. Mani, MD
Cross-Disciplinary Team Leader
Division of Neurology 1

Teresa J. Buracchio, MD
Division Director
Division of Neurology 1

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/

RANJIT B MANI
03/09/2022 02:13:12 PM

TERESA J BURACCHIO
03/09/2022 03:01:34 PM

Summary Review

Date	July 22, 2020
From	Ranjit B. Mani, MD Eric Bastings, MD
Subject	Summary Review
NDA/BLA # Supplement#	NDA 212304 (b) (4)
Applicant	Corium, Inc.
Date of Submission	September 29, 2019
PDUFA Goal Date	July 30, 2020
Proprietary Name / Established (USAN) names	ADLARITY Donepezil Transdermal System
Dosage forms / Strength	5 mg/day 10 mg/day
Proposed Indication(s)	Treatment of mild, moderate, and severe Alzheimer's disease
Action:	Complete Response

1. Background

This New Drug Application (NDA) seeks the approval of ADLARITY® (donepezil transdermal system) for the treatment of mild, moderate, and severe Alzheimer's disease.

This application has been submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, relying in part on the Agency's prior findings of safety and effectiveness for ARICEPT (donepezil) tablets in the treatment of Alzheimer's disease, under NDA 20690.

Donepezil has been marketed in this country under the brand name ARICEPT [Eisai] as a tablet (in 5-mg, 10-mg, and 23-mg strengths), and as an orally-disintegrating tablet (in 5-mg and 10-mg strengths). The 5-mg and 10-mg strengths of the tablet and orally-disintegrating tablet formulations have been approved for the treatment of mild to moderate Alzheimer's disease. The 10-mg strengths of the tablet and orally-disintegrating tablet formulations, and the 23-mg strength of the tablet formulation have additionally been approved for the treatment of moderate to severe Alzheimer's disease. The orally-disintegrating tablet formulation of ARICEPT is no longer marketed. An oral solution formulation of ARICEPT has also been approved in this country, but has never been marketed. NDA numbers for the various approved formulations of ARICEPT are as follows: #20690 (for the 5-mg and 10-mg tablet strengths); #21719 (for the oral solution formulation); #21720 (for the 5-mg and 10-mg orally-disintegrating tablet strengths); and #22568 (for the 23-mg tablet formulation). Generic

formulations of donepezil are also marketed in this country. All approved formulations of donepezil are to be administered once daily, orally. The initial approval of ARICEPT for the treatment of mild to moderate Alzheimer's disease was on November 25, 1996. Please refer to previous Agency reviews of NDAs 20690, 21719, 21720, and 22568 (for the approved brand-name formulations of ARICEPT) for more information about those products.

Under the current application, it is proposed that ADLARITY be administered once weekly. As already noted, oral formulations of donepezil, including those of ARICEPT, are administered once daily.

The development of ADLARITY for the proposed indication has been conducted under Investigational New Drug Application (IND) 129778. Several clinical studies of this product had been conducted outside the United States prior to the submission of IND 129778. The initial interaction between this sponsor and this Agency regarding this development program was through the submission of a Type B Pre-IND meeting package on February 29, 2016, to which the Agency provided written responses only on April 28, 2016. Subsequently, there have been a number of communications between the Agency and sponsor under IND 129778. Among the agreements reached during the course of those communications was that a clinical efficacy study of ADLARITY in patients with Alzheimer's disease would not be required; the Agency had concurred that bioequivalence, on face, and pending FDA review, had been demonstrated between ADLARITY and ARICEPT in a pivotal bioequivalence study.

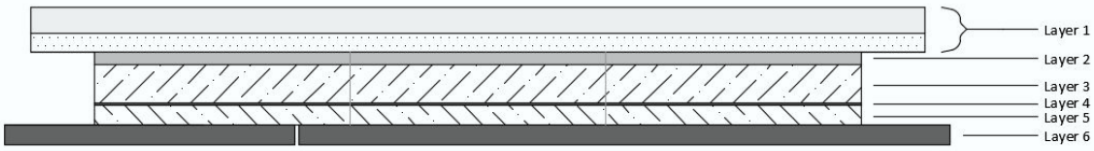
Please note that during this development program, the ADLARITY® transdermal delivery system has earlier been referred to as the Corplex™ Donepezil Transdermal Delivery System.

2. Description And Composition Of ADLARITY Transdermal System

Each ADLARITY transdermal delivery system is intended to continuously deliver donepezil in a dose of either 5 mg/day or 10 mg/day for 7 days. The systems delivering 5 mg/day and 10 mg/day measure 52.5 cm^2 and 105 cm^2, respectively.

Each ADLARITY transdermal delivery system is a rectangular 6-layer matrix-type patch with the following layers: an overlay backing/adhesive layer (tan colored); a separating layer; a drug matrix layer; a microporous membrane layer; a skin contact adhesive layer; and a peel-off blue-tinted release liner.

A cross-sectional schematic (not-to-scale) view of the ADLARITY transdermal delivery system is in the sponsor figure below.



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Layer 6: Release Liner (Removed at the time of use)

3. List Of Clinical Studies Conducted In Support Of This Application

A full list of the clinical studies conducted in support of this NDA is in the following sponsor table.

Study Number	Study Title	Brief Objectives
P-15007	A Phase 1, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Two Formulations of a 7-Day Application of Donepezil Transdermal Delivery System Compared to Oral Administration of Aricept in Healthy Volunteers	Assess initial TDS formulation performance
P-15081	A Phase 1 Parallel Study to Evaluate the Pharmacokinetics (PK), Pharmacodynamics (PD) and Safety of Formulations of a 7-Day Application Donepezil Transdermal Delivery System (TDS) in Healthy Female Volunteers	Formulation Selection
P-16007	A Phase 1 Study to Evaluate the Adhesion, Pharmacokinetics (PK) and Safety of a Seven-Day Application of Donepezil Transdermal Delivery System (TDS) in Healthy Volunteers	Adhesion Optimization
P-15086	A Phase 1, Randomized, Open-Label, 3-Way Crossover, Pilot, Pharmacokinetic Study to Evaluate the Steady State Pharmacokinetics of a Once-Weekly Application of Corplex™ Donepezil Transdermal Delivery System Compared to Daily Oral Administration of Aricept® in Healthy Adult Subjects	Steady state Bioequivalence
P-16011	A Randomized Double-Blind Study to Assess the Skin Irritation and Sensitization Potential of Once-Weekly Corplex™ Donepezil Transdermal Delivery System	Skin Irritation/ Sensitization
P-16012	A Phase 1, Crossover Study to Evaluate the Pharmacokinetics of Corplex™ Donepezil 10 mg Transdermal Delivery System Applied to Different Body Locations	Relative Bioavailability - Application Site (back, thigh, buttock)
P-16039	A Phase 1, 2-Way Crossover Study to Evaluate the Effect of Heat Application on the Pharmacokinetics of Corplex™ Donepezil 5 mg Transdermal Delivery System (TDS) in Healthy Volunteers	Relative Bioavailability – Applied Heat
P-16010	A Study to Assess the Steady State Bioequivalence of Once-Weekly Corplex™ Donepezil 10 mg Transdermal Delivery System Compared to Daily Oral Administration of Aricept®	Safety/Tolerability and Adhesion
P-15086 Sub-Study*	A Phase 1, Randomized, Open-Label, 2-Way Crossover Study, to Compare the Relative Bioavailability of Two Corplex Donepezil Trandsdermal Delivery Systems' Manufactured Using Active Pharmaceutical Ingredient from two Different Suppliers	Relative Bioavailability - API Supplier

**The P-15086 Sub-Study was conducted as an amendment to Protocol No. P-15086.*

4. Discipline Reviews Of This Application

The contents of the individual discipline reviews of this application are summarized below.

4.1 Integrated Quality Review

The Integrated Quality Review of this application was completed by the following primary reviewers: Drs. Rajan Pragani, Andrei Ponta, James Norman, and

Kaushalkumar Dave. Several secondary reviewers and other reviewer staff are also listed. The Application Technical Lead was Caroline Strasinger, PhD.

A serious product quality deficiency was noted during the review of this application: (b) (4) layers could be separated by hand, or even by removing the release liner. As a result, an increased risk of the following has been identified:

- Unintentional overdose.
- Under-dosing and ineffective treatment.
- Potential misuse.
- Accidental exposure to donepezil (for those other than the patient).

The above concerns are explained in more detail in the body of the Integrated Quality Review.

Attempts to correct this deficiency during the course of this review, through multiple communications with the sponsor, have been unsuccessful.

Other product quality deficiencies with this application have also been identified.

The significant product quality-related deficiencies with this application were communicated to the sponsor in a Discipline Review Letter, dated May 4, 2020, and a further email clarification dated May 29, 2020.

This review team has concluded that:

- The sponsor has not provided sufficient Chemistry, Manufacturing, and Controls information to assure the identity, strength, purity, and quality of the drug product.
- The deficiencies in this application preclude labeling discussions and the completion of a labeling review (by the same review team).

This review team has, for the above reasons, recommended that a Complete Response be issued for this application.

Please see the full Integrated Quality Review for more details.

4.1.1 Biometrics Review Of In Vivo Adhesion Data

At the request of the Office of Pharmaceutical Quality, a biometrics reviewer, Chao Wang, PhD, from the Division of Biometrics VI has evaluated the *in vivo* adhesion data for the ADLARITY transdermal system in the clinical studies P-15086, P-16007, P-16010, and P-16012. This review was completed on May 4, 2020.

This review has concluded that the probability of an ADLARITY transdermal system maintaining adhesion was at least 75% for the entire wear period. The review further states that the available data suggest that adhesion is best when that transdermal system is applied to the back, with less adhesion when that system is applied to the thigh, and even less adhesion when that system is applied to the buttock.

Please see the full text of that review for more details.

4.2 Clinical Review

David A Hosford, MD, PhD, was the clinical reviewer of this application. His review was completed on July 7, 2020.

Please see his full review for the clinical details of this application.

Among his main observations were the following:

- The safety and tolerability of ADLARITY were satisfactory, extending to low skin irritation and sensitization, and to gastrointestinal, central nervous system, and other systemic adverse events.

- No clinical efficacy studies of ADLARITY were conducted, as bioequivalence has been demonstrated between that product and ARICEPT tablets.

Dr. Hosford has, however, recommended against the approval of this product, as the patch (b) (4) had a tendency to separate at times (b) (4), as noted by the product quality review team. As a result, patients or caregivers may be accidentally exposed to donepezil if they touch the product (b) (4); and the intended daily dose may not be delivered.

4.3 Clinical Pharmacology Review

The Office of Clinical Pharmacology review of this application was completed by Dr. Hristina Dimova, together with Drs. Vishnu Sharma, Angela Men, and Atul Bhattaram, on May 28, 2020.

This review team has noted that bioequivalence was established at steady state between the ADLARITY once-weekly transdermal system and ARICEPT in the pivotal clinical pharmacology study P-15086, for both C_{max} and $AUC_{0\text{-}tau}$.

This review team has also noted that the manufacturing process used for the ADLARITY transdermal system product investigated in Study P-15086 was not the same as that proposed for the ADLARITY commercial product. Thus, further pharmacokinetic data is needed to bridge the product used in pivotal study P-15086 and the commercial ADLARITY product.

This review has further noted that a consultation request was sent to the Office of Scientific Inspections and Surveillance requesting clinical and bioanalytical site inspections for Study P-15086. However, the Office of Scientific Inspections and Surveillance determined that such inspections were not warranted, as the same sites had been inspected recently.

This review team has found the information submitted in support of this application not to be acceptable. The same review team has also stated that discussions of labeling are premature.

For further details, please refer to the in-depth discussion in the Clinical Pharmacology review.

4.4 Nonclinical Review

The nonclinical review of this submission was completed by David Hawver, PhD, on July 20, 2020.

Dr. Hawver has reviewed the results of the special local toxicity studies of ADLARITY® (also referred to as the Corplex Donepezil Transdermal System in his review). Please see the text of his review for a detailed description of those results.

He has concluded that the nonclinical data submitted with this application adequately support the approval of ADLARITY® for the treatment of patients with Alzheimer's disease.

4.5 Labeling Comprehension Study Report Review

This review was completed on June 16, 2020, by Carol Holquist, RPh, of the Division of Medical Error Prevention and Analysis, and has addressed the results of the sponsor's Human Factors Labeling Comprehension Study evaluating the clarity and effectiveness of the labeling instructions for application, removal and disposal of the ADLARITY transdermal system.

On account of multiple deficiencies further described in this review, the reviewer was unable to conclude that sponsor's Human Factors Labeling Comprehension

Study confirmed patients' and caregivers' understanding of the safe and effective application, removal, and disposal of the proposed ADLARITY transdermal system.

The deficiencies in the Human Factors Human Factors Labeling Comprehension Study are described in detail in Ms. Holquist's review.

4.6 Label, Labeling, And Packaging Review

This review was completed on April 16, 2020, by Denise Baugh, PharmD, BCPS, of the Division of Medical Error Prevention and Analysis.

A number of recommendations were made in this review regarding the contents of the Prescribing Information and the packaging for this product. Please see that review for more details.

(As noted elsewhere in this summary review, draft labeling is not to accompany the action letter for this application).

4.7 Proprietary Name Review

This review was completed on November 19, 2019, by Beverly Weitzman, PharmD, of the Division of Medical Error Prevention and Analysis.

This review has concluded that the proprietary name ADLARITY is acceptable for this product.

5. Conclusion And Recommendation

The sponsor has not provided sufficient information in this application to support the approval of ADLARITY (donepezil transdermal system) for the treatment of mild, moderate, and severe Alzheimer's disease.

The salient deficiencies in this application extend to:

- A product quality defect: a failure of key layers in the ADLARITY transdermal system (b) (4).

- A lack of pharmacokinetic data that might bridge the commercial ADLARITY formulation with that used in the pivotal bioequivalence study P-15086.

A Complete Response letter will therefore be issued for this application.

rbm

cc:
HFD-120
IND

APPEARS THIS WAY ON ORIGINAL

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/

RANJIT B MANI
07/22/2020 12:56:48 PM

ERIC P BASTINGS
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