CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212304Orig1s000

OTHER ACTION LETTERS

U.S. FOOD & DRUG ADMINISTRATION

NDA 212304

COMPLETE RESPONSE

Corium, Inc.
Attention: (b) (4)

Dear Dr. (b) (4):

Please refer to your New Drug Application (NDA) dated September 30, 2019, received September 30, 2019, and your amendments, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ADLARITY (donepezil transdermal system). We also refer you to the Discipline Review Letter (DRL) dated May 5, 2020 and the clarifying communication sent May 29, 2020 (response to your request for a clarifying teleconference).

We also acknowledge receipt of your amendments dated April 28, 2020, April 29, 2020, May 1, 2020, May 22, 2020, June 1, 2020, June 15, 2020, June 30, 2020, and July 8, 2020, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address those issues.

The list below is inclusive of requests communicated in the Discipline Review letter dated May 4, 2020, and additional issues identified after May 4, 2020. This list serves as a comprehensive list of deficiencies and additional comments for this Complete Response. **If significant changes are made to the product (e.g., in formulation, design, and size) to address the Complete Response deficiencies identified below, additional studies such as *in vivo* adhesion studies, other clinical assessments, and/or redevelopment of some quality test methods and acceptance criteria may be necessitated.**

Complete Response Deficiencies

1. [redacted] the TDS can be easily separated [redacted] and as such is a major product quality, use, and safety concern.

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)

Recommendation to Address Deficiencies:
To address this concern, you should [redacted] to the extent that the product cannot be peeled apart by hand (i.e., when peeled apart by hand, the membranes are significantly damaged or destroyed when the attempt is made).

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:
   - [redacted]

   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 [redacted]% over 24 months. The 48-hour time point results decrease [redacted]% over 24 months. The 168-hour time point results decrease [redacted]% over 24 months. The provided *in vitro* skin permeation data and the limited *in vivo* pharmacokinetics data (of up to six-month-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 [redacted] 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.

Recommendation to Address Deficiencies:
To demonstrate the product at the beginning of shelf life is equivalent to product at the end of shelf life, you should conduct a bioequivalence study on product near the beginning of shelf life comparing it to product near the end of the proposed shelf-life. Alternatively, you should develop a formulation which exhibits greater stability with respect to excipient degradation, migration, (b) (4), etc. We also refer you to Complete Response deficiency #3, which recommends a new bioequivalence study with oral Aricept, and Complete Response deficiency #1, which may result in a reformulation. As such, you may want to consider incorporating product that is freshly manufactured (<6 months in age) and product that is nearing the end of shelf-life (>12 months in age) in your trial if the reformulated product is not expected to exhibit greater stability than the current formulation.

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 (Page 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 an impact on (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, active product ingredient 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.

   Recommendation to Address Deficiencies:
   To address this concern, you should conduct a new bioequivalence (BE) study with oral Aricept utilizing the proposed commercial product/manufacturing process. Please note that should significant changes to the formulation or manufacturing

process be made to address other Complete Response Deficiencies, the BE study should utilize product that includes those changes.

4. [redacted] (b) (4)

   Recommendation to Address Deficiencies:
   [redacted] (b) (4)

5. During a recent inspection of the [redacted] (b) (4) manufacturing facility, our field investigator conveyed deficiencies to the representative of the facility.

   Recommendation to Address Deficiencies:
   Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional Comments

The following comments are not approvability issues, but should be addressed in the resubmission of this application.

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.*" You should provide updated versions of these sections.

2. An incorrect FEI number was provided in the FDA Form 356h for [redacted] (b) (4). You should provide an updated copy of the FDA Form 356h.

3. The amendment to the NDA, submitted on April 28, 2020, 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 March 31, 2020, to demonstrate that active product ingredient (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. You should provide additional study data that justify that API particle size does not impact [redacted].

5. [redacted]

6. [redacted]

7. As part of the amendment dated April 10, 2020, you have updated the release liner [redacted]. You should also:
   a. Provide data demonstrating that the [redacted] is robust ([redacted] and remains unchanged during storage (e.g., [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] psi for the 5 mg/day strength and NLT [redacted] psi for the 10 mg/day strength) is based on a combination of release and stability data of 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] in the primary registration batch 38132B. [redacted] this should be further clarified.

10. We note that you have committed to addressing the following questions, but responses are currently pending:

a. Question 2 from our December 31, 2019, Information Request: Develop a method for the separation strength of [redacted] (b) (4) [redacted]). Monitor separation strength on release and stability of the drug product. Set and justify the associated acceptance criterion.

b. Question 6b from our December 31, 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 our March 9, 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. We are concerned with the proposed oral-to-transdermal system switch strategy for the 5 mg/day treatment. For the 5 mg/day treatment, donepezil concentrations during the first 10 days after oral-to-transdermal system switch were observed to be lower than the oral $C_{min,ss}$ of 20.6 ng/mL. The clinical relevance of these lower concentrations is not known, and to ensure clinical benefit, oral supplementation with 5 mg/day ARICEPT may be required during the first 2 weeks of oral-to-transdermal system switch. Additional simulations must be conducted to derive an appropriate oral-to-transdermal system switch for 5 mg/day treatment.

12. Due to the issue stated above related to ease of separation of the laminate layers, we have serious safety concerns that could arise if layer separation occurs during the use of the ADLARITY transdermal system. If layer separation occurs while patients are wearing the ADLARITY transdermal system, alterations in donepezil dosing may occur. If the patient or caregiver touches any exposed layers that contain donepezil, unintended exposure to donepezil may occur. If the active layer segments can be easily separated by hand, patients or caregivers may elect to modify their dose (e.g., only applying 4 of the 9 segments), or may choose to apply the smaller segments to locations on the body not previously studied (e.g., for aesthetic preference). Each of these clinical situations represents an unacceptable safety risk.

13. Due to the issue stated above related to ease of separation of the laminate layers, we indicated to you on January 31, 2020, that "*labeling enhancements will not address the inherent product design flaw and the risk of the separation of* [redacted] (b) (4) *the TDS* [redacted] (b) (4)" and that a labeling comprehension study (LCS) is not the appropriate mechanism to address the concerns. We note, however, that you conducted an LCS and we have reviewed

the contents of that April 10, 2020, submission. Our review determined that there are significant methodology concerns with your LCS that raise concerns with interpretation of the study results. The patient user group did not include a representative sample size of 15 study participants, the simulation of transdermal system application did not replicate real world use as patients and caregivers applied the transdermal system to an easel rather than the application areas described in the Instructions for Use, and based on your response to our Information Request for product samples, the intent-to-market product was not used in the LCS. Moreover, the errors observed in this study indicate the labeling did not provide assurance that patients and caregivers could adequately identify adhesive squares that remained on the skin or on the liner. Thus, we are unable to conclude that the LCS confirms that the product labeling addresses the risks associated with the separation of (b) (4) the transdermal system (b) (4). Therefore, we remain concerned that labeling enhancements alone will not minimize the risk to patients and caregivers if (b) (4) the transdermal system separates (b) (4).

PRESCRIBING INFORMATION

A. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

   If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

CARTON AND CONTAINER LABELING

A. You should submit draft carton and container labeling revised as follows:

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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

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

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

3. The expiration date format is not defined on the container label and carton labeling. To minimize confusion and reduce the risk for deteriorated product medication errors, identify the format you intend to use. The Agency recommends that the human-readable expiration date on the product package label include a year, month, and non-zero day. Additionally, the Agency recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the product package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. A hyphen or a space may be used to separate the portions of the expiration date.

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

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

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

(b) (4)

7. We note the presence of a placeholder for the lot number and expiration date on the container labels and carton labeling. However, it is unclear how the lot number and expiration date will appear. Ensure that there are no other numbers located in close proximity to the lot number where it can be mistaken as the lot number[4] and ensure the lot number is clearly differentiated from the expiration date.[5]

8. The color scheme of the 10 mg/day strength statement ((b) (4)) and the proprietary name (ADLARITY) appear in the same (b) (4) color ((b) (4)). The use of the same (b) (4) color font for the proprietary name and one of the product's strengths minimizes the difference between the two strengths, which may lead to wrong strength selection errors. You should revise the font color of the proprietary name or revise the color scheme of the 10 mg/day strength, so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.

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

10. You should add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**."

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

1. The *"Rx only"* statement appears more prominent than other important information on the Principal Display Panel (PDP). Per our guidance, the proprietary name, established name, product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the

[4] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.
[5] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

PDP[6]. Ensure the *"Rx only"* statement does not compete in prominence with the aforementioned critical information. Consider decreasing the font size and relocating the *"Rx only"* statement to the top or bottom of the PDP or address this concern by other means.

2. The strength statement appears twice on the PDP, which is unnecessary and clutters the label. You should streamline the strength statement to appear once on the principal display panel as "*xx mg/day*".
3. The statement "*For Transdermal Use Only*" is not prominent and may be overlooked, which may pose risk of wrong route of administration or wrong technique medication errors. You should improve the prominence of the statement "*For Transdermal Use Only*" to emphasize proper use of this product and to ensure it is not overlooked. To accomplish this, consider (b) (4) or address this concern by other means.
4. The net quantity statement (i.e., Contains 1 system) is located in close proximity to the product strength. From postmarketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. You should relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel.

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

1. The transdermal system disposal instructions on the carton labeling lack the important warning to dispose out of the reach of pets. We are concerned that this may result in inappropriate disposal, which could result in accidental exposure by pets. Revise the statement " (b) (4) to read ' (b) (4) wherever it appears in the disposal instructions (for example, on the back panel under " (b) (4) ').
2. As presented, there is a "flap' which appears in the lower right-hand corner of the PDP. The intent of this "flap" is unclear (e.g., is this a peel-off label to access additional product information or a graphic design?). You should clarify the intent of this "flap."

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

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

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

1. We note the presence of [redacted] (b) (4) which overlaps the product strength ("*XX mg*") near the bottom of the principal display panel. We are concerned that users may misinterpret this [redacted] (b) (4) to mean that 4 systems are required for a XX mg dose. To avoid confusion, you should remove this [redacted] (b) (4) from the principal display panel, or address this concern by other means.
2. As currently presented, there is no placeholder for a product identifier on the carton labeling. In September 2018, the Agency released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[7] The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review that draft guidance which is available at the following link:

   https://www.fda.gov/media/116304/download

   If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the human-readable and machine-readable (2-D data matrix barcode) product identifier to the carton labeling.
3. It is unclear whether pouches are intended for individual dispensing. The carton labeling contains important safety information that may not be available to users if pouches are dispensed individually. You should clarify whether pouches are intended for individual dispensing or whether they should be dispensed in the sealed

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

carton. If the latter, you should consider revising the carton labeling to state "*Dispense in this sealed carton*" on the principal display panel, or address this concern by other means.

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

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

F. Instructions for Use (IFU)

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

PROPRIETARY NAME

Please refer to correspondence dated September 19, 2019, which addresses the proposed proprietary name, ADLARITY. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug/product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, you should incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the re-tabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug/product. Include an updated estimate of use for drug/product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting,

submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Teresa Wheelous, Regulatory Project Manager, at teresa.wheelous@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD.
Director (Acting)
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

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/

ERIC P BASTINGS
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